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ANTIMALARIAL DRUGS IN NIGERIA: RESULTS OF A NEW SURVEY

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The first survey of the use of antimalarial drugs in Nigeria (Bruce-Chwatt and Bruce-Chwatt, 1950) provided data on some special aspects of prophylaxis and treatment of malaria in this the largest British dependency in West Africa. A similar investigation by Nicol (1953) reported on the experience of the expatriate population in Lagos and discussed the value of various protective antimalarials in Nigeria.

Chemotherapy of malaria has progressed a great deal during the past decade, and a resurvey of the situation in Nigeria was called for. It was especially timely, because the difficulties of malaria eradication in holoendemic areas of tropical Africa by residual insecticides alone have aroused more interest in the possibilities offered by chemotherapy (W.H.O., 1957). Moreover, it was thought that an assessment of the situation might be of value, as some new trends in the use of antimalarial drugs in Nigeria reflect the profound socio-economic changes seen in West Africa to-day.

This paper deals mainly with the small and transient but well-defined group of the non-immune expatriate population; problems of malaria in the indigenous population of Nigeria will be presented at a future date. Nevertheless, a considerable amount of information pertaining to chemotherapy of malaria in Africans was collected and is reported here.

The total population of Nigeria at the 1952–3 census was 31½ millions, and it was estimated that it increases at the rate of nearly 2% per annum.

The non-African population in Nigeria is distributed unevenly and its composition is constantly changing because of an estimated turnover (due to home leave) of about 30% during the year. This population numbered 16,700 in 1953 and nearly 18,000 in 1956. Of the total of 17,953 expatriates (in mid-1956), 30% were residents in the Federal Territory of Lagos, 31% were in the Northern Region, 20% in the Western Region, and 20% in the Eastern Region and the Southern Cameroons. The overall national composition of the non-African civilian population of Nigeria at the census was approximately as follows: 60% were British; 3% Commonwealth citizens, including Indians; 6% Americans; 9% Syrians and Lebanese; 3% French; 3% Dutch; 3% Irish; and the remaining 13% belonging to various other nationalities (Nigeria, 1954).

There are few reliable figures referring to the incidence of malaria in the expatriate population of the Federation of Nigeria. The reasons for it were discussed before (Bruce-Chwatt and Bruce-Chwatt, 1950), and the situation has not changed.

Reliable diagnosis of malaria in non-immunes in West Africa is not easy for reasons opposite to those discussed with regard to malaria of the indigenous population. The attitude of the individual medical officer towards this problem varies considerably between two extremes: (*a*) labelling as malaria any disease with vague clinical symptoms which might or might not be due to the plasmodial infection, and (*b*) recognizing malaria only on the basis of a confirmatory report of a blood examination. Errors are bound to be committed in either case, and some striking differences between two successive annual rates of malaria in the same locality are often due to a change of medical officers.

An additional difficulty arises from the universal use of antimalarial drugs by the expatriate population; this greatly decreases the chance of finding parasites in the blood, and the diagnosis is then made by presumption when the symptoms respond to a tentative specific treatment. Thus the records of malaria incidence among expatriates in Nigeria are not more than estimates subject to many errors.

INFORMATION ON MALARIA AND ANTIMALARIAL DRUGS FROM TWO QUESTIONARIES

Two years ago it was decided that some more reliable information on the incidence of malaria in Nigeria and on the value of modern antimalarial drugs could perhaps be obtained through suitably designed questionaries, similarly to what had been done in 1950. It was intended to have two polls of opinion: one addressed to the medical profession in Nigeria, the other to a large though selected group of the residential population of Lagos which relies on routine drug prophylaxis for individual protection against malaria.

The medical questionary asked the following ques-

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tions: number, sex, and age of expatriates in the relevant station; number of cases of malaria during the year; type of prophylactic drug taken by the patients and regularity of administration; type of treatment favoured by the medical practitioner; evidence of toxic effects during prophylactic or therapeutic regimen; views on malaria prophylaxis and treatment in Africans and expatriates.

The non-medical questionary asked for information on the following: nationality, age, and sex; duration of stay in Nigeria and in Lagos; type of antimalarial drug taken and dosage; on whose advice and how regularly; reasons for change of drug if any; incidence of malaria and by whom diagnosed.

In July, 1956, the Federal Malaria Service dispatched two questionaries. One, numbering 380 copies, was addressed to medical officers in Government stations and medical missions, and to private practitioners; the other was sent to 3,200 householders whose names appeared in 1956 in the official "residential list" of Lagos township.

The response to the questionary forwarded to 380 medical officers in Nigeria produced 146 complete replies, an overall percentage of 38.5. Of these replies, 128 came from the three Regions of Nigeria and 18 from Lagos. The expatriate population, under the medical care of 128 medical officers stationed outside the Federal Territory of Lagos, who answered the questionary, amounted to 6,859, which represents approximately 54% of the total expatriate population of Nigeria residing outside the Federal Territory in 1956.

Of the 3,200 questionaries sent out to the "residential" population of Lagos, 1,026 were returned. Of these, 1,016 gave information in respect of 2,222 persons, distributed as shown in Table I.

TABLE I.—*"Residential" Population of Lagos. Replies to the Questionary by Race and Age Group*

	Adults (15 Years) and Over)	Children 2–14 Years	Infants Under 2 Years	Total
Europeans (=Caucasians) ..	1,557	395	75	2,027
Africans	103	56	12	171
Others	20	3	1	24
Total ..	1,680	454	88	2,222

The collected data were coded, put on marginal punch-cards, and numerically assessed; they constitute the main subject of this paper and represent two polls of opinion—one medical, covering the whole country, and the other non-medical, limited to Lagos.

Incidence of Malaria

The two questionaries provided some interesting data on the incidence of malaria in the expatriate population on a sample which amounts to 49% of the total 1956 population of expatriates in Nigeria (Table II).

Table II quotes for the three regions of Nigeria the number of cases of malaria duly diagnosed and reported by medical practitioners. The incidence of malaria in the Federal Territory of Lagos is quoted from the replies forwarded by the "residential" population and refers only to malaria diagnosed by a medical officer. Reports of "suspected malaria" (a total of 97) not seen or not confirmed by a doctor were not included, as it was felt that many of the symptoms could have been easily confused with undetermined or minor ailments.

As pointed out previously, the diagnosis of malaria in expatriates in tropical Africa is, paradoxically enough, not easy (even when made by medical practitioners), and the figures quoted must be interpreted with caution, although they are the best data that can be obtained in the circumstances.

Table II indicates that, as one would expect, the incidence of malaria in non-immunes is much less in the mainly urban population of the Federal Territory of Lagos than in the regions, which, with the exception of a few main centres, are predominantly rural areas. Moreover, the overall figures indicate that the incidence of malaria in the expatriate population of Nigeria fell from 225 per 1,000 in 1949 to 142 per 1,000 in 1956. The low mortality from malaria in the expatriate population is striking. There was one fatal case of blackwater fever in a Syrian merchant, following an intramuscular injection of quinine. One death due to cerebral malaria was recorded in a European child, but no details of this case are available.

With regard to the "residential" population of Lagos the data collected during the present survey indicate that the malaria incidence of expatriates decreased during the past eight years from 149 per 1,000 in 1948 to about 60 per 1,000 in 1956.

Thanks to the ready co-operation of the Army medical authorities, it was possible to obtain valuable data on the incidence of malaria in the British military personnel serving in Nigeria and in their families. This group numbers about 1,000, of whom 60% are male adults. The incidence of malaria in the British Army personnel, including the families, was 25 per 1,000 in 1956 (data incomplete) and 35 per 1,000 in 1957. Both figures are well below the rates estimated for the civilian expatriate population and confirm the impression that a number of cases of malaria in expatriates are due to a lapse in the regular routine of drug taking.

Comparative Therapeutic Value of Antimalarial Drugs

From the 146 replies to the questionary sent by the members of the medical profession there seems to be nothing approaching a standard treatment of malaria in Nigeria. Although the replies revealed many variations of treatment and a large number of combinations of antimalarial drugs a general pattern was discernible.

For the emergency treatment of severe malaria mepacrine and chloroquine are used with equal frequency, mainly by intramuscular injection; quinine is also used, though somewhat less often, by the intramuscular and occasionally by the intravenous route. The most common single adult dose of quinine injections is 10 gr. (650 mg.); the relevant doses of chloroquine and mepacrine are 200 mg. of base and 300 mg. of base respectively. Because of the frequency of toxic reactions in infants and small children, quinine and chloroquine (in suitably graded dosage) are preferred to mepacrine in paediatric practice.

For peroral treatment of moderately severe malaria chloroquine is the most-favoured single drug, selected by 60% of all medical practitioners, with mepacrine second (24%), amodiaquine third (14%), and quinine fourth (2%).

TABLE II.—*Malaria Morbidity in the Expatriate Population in Nigeria in 1956*

	Men			Women			Children			Total		
	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000	No.	Malaria	Per 1,000
Regions	3,565	628	176	1,977	311	157	1,317	202	153	6,859	1,141	166
Lagos	895	69	78	662	30	45	470	19	40	2,027	118	58
Total ..	4,460	697	157	2,639	341	129	1,787	221	124	8,886	1,259	142

A few correspondents placed much faith in the therapeutic value of proguanil, and two among them regarded pyrimethamine (at 100 mg. in 36 hours) as a good drug for the treatment of malaria.

Many medical practitioners treat ordinary attacks of malaria by a single intramuscular injection of quinine or mepacrine followed by oral administration of chloroquine or mepacrine or amodiaquine. A few use such combinations as amodiaquine–pyrimethamine, mepacrine–proguanil, etc.

The mean dosage of oral chloroquine is 1.8–2.1 g. of base in three to five days, of mepacrine 1.6–3.0 g. in three to five days, and of amodiaquine 1.2–1.4 g. in four days.

Many medical men adopt the logical principle that the drug used for treatment must be different from that used for prophylaxis. All of them agree that malaria in Africans past early childhood responds well to a less-sustained treatment than the disease seen in non-immunes.

Comparative Value of Prophylactic Antimalarial Drugs

(1) Medical Questionary

Out of 146 replies to the medical questionary, 97 (67%) favoured proguanil; of these, 52 advocated the standard dosage at 100 mg. daily, while 45, mainly from the Northern Region, preferred the daily dosage of 200 mg. Twenty-two replies (15%) gave pyrimethamine at 25 mg. or 50 mg. once a week as the best protective antimalarial. Twenty (14%) advocated chloroquine at two doses once a week totalling 300 mg., though a few preferred a weekly dosage of 600 mg. Three medical men considered that mepacrine and amodiaquine were the most reliable protective antimalarials, while two correspondents were staunch defenders of the "good old quinine."

In attempting to assess the protective value of antimalarials it was found from the medical questionary that the number of so-called "break-throughs" reported in people who were taking various drugs was roughly the same as the different ratios of their uses. Thus, of the break-throughs, 75% were reported in takers of proguanil (mainly in those whose daily dose was 100 mg.), 8% in takers of pyrimethamine, 10% in takers of chloroquine, 4% in takers of quinine, and 1% in takers of mepacrine or amodiaquine. In other words, it was alleged that none of the drugs was 100% effective in preventing attacks of malaria.

As the regularity and adequacy of prophylactic drug administration was not always certain, the reports on break-throughs should not be taken too literally. The fact that these break-throughs occurred roughly in proportionately the same number of people taking various antimalarials suggests that many of them were due to an inadequate prophylactic regimen, while others were due to various febrile conditions.

There is evidence of two widely differing attitudes of the medical profession in Nigeria with regard to the use of prophylactic antimalarials in Africans. While 20 doctors maintained that mass prophylaxis for the indigenous population is neither necessary nor beneficial because of the possible loss of acquired tolerance to malaria, 25 doctors were strongly in favour of drug prophylaxis, especially in some selected indigenous groups such as expectant mothers, schools, labour camps, etc.

An interesting observation came from a large leprosy centre directed by a mission: 500 patients were kept for one year on a weekly pyrimethamine prophylaxis, and this not only reduced the incidence of malaria but apparently also that of lepra reaction after sulphones. For prophylactic administration in African communities mepacrine, proguanil, or pyrimethamine once a week was favoured.

A few industrial organizations have adopted the policy of regular drug prophylaxis of their indigenous staff, and reported satisfactory results either because of apparent decrease of sickness or on account of better public relations. The Army has recently introduced a regular prophylactic regimen for all Nigerian members of the Forces, including their families. The drug selected was pyrimethamine at 25 mg. once a week.

(2) Non-medical Questionary

The results of the non-medical "residential" questionary are shown in Table III and refer to 2,027 European (=Caucasian) residents. The replies of 171 African and 24 Indian residents represent a very small group, and for the sake of convenience were grouped together. The replies showed that proguanil was used by 68% of the residential population of Lagos. It was the most popular drug in all races, except for infants and to a less extent for children, in whom it was replaced by pyrimethamine, used by 20% of the public. Chloroquine was the third (6%) most popular prophylactic, while amodiaquine was used by 0.5% of people; mepacrine, which in a previous survey was still being taken by 10.6% of the population, has almost completely dropped out of favour, being taken by only 22 persons (1%). Quinine, which in 1950 was taken by 18.7% of expatriates, has dropped to 4%—mostly "old coasters," though it is still favoured by some, particularly for children and infants. No drug, except perhaps mepacrine, showed any significant difference by sex: this antimalarial is rarely taken by women.

TABLE III.—*Selection of Protective Antimalarial Drugs by the "Residential" Population of Lagos in* 1956

	Adults		Children		Infants		Total	%
	No.	%	No.	%	No.	%		
Europeans:								
Proguanil ..	1,141	73·3	254	64·3	33	44·0	1,428	70·4
Chloroquine ..	92	5·9	9	2·3	2	2·7	103	5·1
Pyrimethamine	245	15·7	126	31·9	36	48·0	407	20·1
Mepacrine ..	12	0·8	—	—	—	—	12	0·6
Quinine ..	59	3·8	6	1·5	4	5·3	69	3·4
Amodiaquine	3	0·2	—	—	—	—	3	0·1
No drug ..	5	0·3	—	—	—	—	5	0·2
Total ..	1,557	100	395	100	75	100	2,027	100
Africans and Indians:								
Proguanil ..	56	45·5	23	39·0	3	23·0	82	42·1
Chloroquine ..	21	17·1	7	11·8	1	7·7	29	14·9
Pyrimethamine	17	13·8	5	8·5	5	38·4	27	13·7
Mepacrine ..	7	5·7	3	5·1	—	—	10	5·2
Quinine ..	6	4·9	13	22·0	4	30·9	23	11·8
Amodiaquine	6	4·9	3	5·1	—	—	9	4·6
No drug ..	10	8·1	5	8·5	—	—	15	7·7
Total ..	123	100	59	100	13	100	195	100

Thus proguanil is shown to be the drug of choice; but where ease of administration is of particular importance, as in children and infants, pyrimethamine replaces it as a favourite. It will be noted from Table III that five Europeans and 15 Africans stated that they take no antimalarials at all. Of the Europeans, one man said that "mosquitoes did not seem to bite him," another said it "was not required in Lagos," one woman put her faith in homoeopathic remedies, and two women stated that all antimalarials upset their digestion.

The "residential" questionary attempted to investigate the incidence of malaria in the non-immune population of Lagos on the basis of the information received from 2,027 expatriates.

The reported cases of illness attributed to malaria were divided into three groups: (1) malaria diagnosed as such by a doctor; (2) suspected malaria—not seen by a doctor; and (3) "fever." The results are set out in Table IV, which shows that the so-called "break-throughs" of malaria occur with all drugs in about 6% of persons.

The first and second most favoured dosage schedules of the main drugs taken by adults of the sample of the Lagos residential population are shown in Table V. The percentages in this table refer to the number of people taking the particular drug. The dosage for children is lower by approximately one half.

TABLE IV.—*Incidence of "Malaria" in Expatriate Takers of Antimalarials in Lagos*

	Diagnosed Malaria		Suspected Malaria		"Fever"		Protected	
	No.	%	No.	%	No.	%	No.	%
Proguanil:								
Adults ..	72	6·3	51	4·5	146	12·8	872	76·4
Children ..	15	5·9	12	4·2	32	11·2	228	79·5
All ages ..	87	6·1	63	4·4	178	12·5	1,100	77·0
Chloroquine:								
Adults ..	5	5·4	4	4·3	10	10·9	73	79·4
Children ..	2	22·2	—	—	—	—	9	77·8
All ages ..	7	6·8	4	3·9	10	9·7	82	79·6
Pyrimethamine:								
Adults ..	18	7·4	20	8·2	24	9·8	183	74·6
Children ..	2	1·6	6	3·7	22	13·5	132	81·5
All ages ..	20	4·9	26	6·4	46	11·3	315	77·4
Mepacrine:								
Adults ..	—	—	1	8·3	3	25·0	8	66·7
Children ..	—	—	—	—	—	—	—	—
All ages ..	—	—	1	8·3	3	25·0	8	66·7
Quinine:								
Adults ..	4	6·8	3	5·1	5	8·5	47	79·6
Children ..	—	—	—	—	—	—	10	100·0
All ages ..	4	5·8	3	4·3	5	7·2	57	82·7
Amodiaquine:								
Adults ..	—	—	—	—	—	—	3	100·0
Children ..	—	—	—	—	—	—	—	—
All ages ..	—	—	—	—	—	—	3	100·0
Total:								
Adults ..	99	6·4	79	5·1	188	12·1	1,186	76·4
Children ..	19	4·1	18	3·8	54	11·5	379	81·0
All ages ..	118	5·8	97	4·8	242	12·0	1,565	77·4

TABLE V

Drug	Modal Dose	Second Mode
Proguanil	7 tablets weekly—86%	14 tablets weekly—7%
Chloroquine	2 tablets weekly (300 mg.)—51%	3–4 tablets weekly (450–600 mg.)—42%
Pyrimethamine	1 tablet weekly—74%	2 tablets weekly—22%

Optimum Dose of Antimalarial.—It was found that there was no clear-cut correlation between the incidence of "malaria" and variation in the weekly dosage. Chloroquine, of which the most popular doses are two and three tablets a week for adults, and one and two tablets a week for children, shows the expected result—that is, 92.3% protection on the higher dose and 74.5% on the lower dose. This difference, however, just fails to reach statistical significance at the 5% level ($p=0.0543$ by Fisher's exact test). Amongst adults taking proguanil the converse is the case: those taking the modal dose of seven tablets a week are 77.2% protected, whereas those taking 14 tablets a week show 67.5% protection. This difference again just misses significance at the 5% level ($t=1.93$, with 1,051 degrees of freedom). Similar unexpected findings refer to samples of children taking proguanil at half-tablet (50 mg.) daily or one tablet (100 mg.) daily respectively. The same applies to two groups of adults: one on one tablet (25 mg.) of pyrimethamine and the other on two tablets (50 mg.) once a week. In children pyrimethamine shows the expected trend: 80.1% protection on the lower dose, and 84.7% on the higher.

The paradox of the higher dose giving the lower degree of protection is of interest though of limited importance. The ambiguous results of this part of the investigation are obviously due to neglect of numerous variables such as body weight, exposure to infection, and, last but not least, vagaries in the diagnosis of malaria.

Regularity in taking a drug is of prime importance for successful chemoprophylaxis, and a specific point was included in the questionary. Only 10 Europeans out of 2,022 confessed to irregularity in taking their antimalarials (from our personal experience, one might express some doubts about the reliability of this particular information). Amongst Africans, no fewer than 56 (32.7%) were irregular takers.

Reasons for choice of a particular drug were asked for, and the answers showed two primary reasons: proguanil was "officially recommended" to 57% of people by a doctor or an employer, while pyrimethamine was recommended to 11% and chloroquine to 16%. "Ease of administration" favoured pyrimethamine in 67% of its takers and proguanil in 33%.

(3) Toxic Effects of Antimalarial Drugs

Replies referring to side-effects of antimalarial drugs were of considerable interest. The results of the survey are discussed on the basis of data from the two questionaries grouped separately for therapeutic and suppressive usage.

Medical observations on toxic reactions due to the therapeutic or protective administration of antimalarials are summarized below. It must be admitted that many side-effects associated with the prophylactic regimen (headache, insomnia, gastro-intestinal disturbances, depression, etc.) were so vague that the relationship between their frequency and the taking of a specific antimalarial was unconvincing.

Quinine.—The symptoms of cinchonism after high dosages of this drug are so well known that they need not be reported here. There was one case, however, of a sciatic nerve injury and paralysis after an intramuscular injection and one fatal case following an intravenous administration of the drug to a child. Intramuscular injections of quinine, nowadays much less common than before, were still advocated by 25 medical officers, particularly in severe malaria in children, apparently with very few local abscesses following the injection. There was one fatal case of blackwater fever following an intramuscular injection of quinine in a Syrian patient and five cases of "blackwater fever" in African children given irregular doses of quinine.

Mepacrine.—The most striking toxic effect of this drug, when given to infants and children up to 3 years of age, was an epileptiform seizure after the intramuscular injection of 100–150 mg. of mepacrine musonate. A total of 37 of these dramatic sequelae with 29 deaths were reported by 18 medical officers, including one case in the Army. The symptoms set off within 10 to 15 minutes after the injection, and consist of sudden clonic and tonic convulsions, dyspnoea, cyanosis, loss of consciousness, and either death or recovery within one to two hours. Two such cases with clonic convulsions of legs or one arm lasting for 20 minutes were observed in adults soon after the injection of 300 mg. of mepacrine. Cases of psychosis, mainly in adults, following the oral administration of mepacrine were reported by 36 medical officers. The incidence of this side-effect cannot be computed, but two correspondents assessed that it averaged 2% of people treated with mepacrine given at the standard dosage. In one small station four patients who were given rather high but not excessive doses of mepacrine developed mental symptoms, some of them of maniacal nature. Other side-effects ascribed to mepacrine were gastric symptoms with vomiting (4), gluteal abscess after intramuscular injection (3), and dermatitis (3).

Chloroquine.—Two epileptiform fits similar to those observed after parenteral mepacrine were reported following an intramuscular injection of 100 mg. of chloroquine—one in an infant, the other in a child of 18 months; one case recovered. The standard therapeutic regimen of chloroquine was followed by a number of side-effects. Vomiting and abdominal discomfort were most commonly reported; the next two common complaints were pruritus and blurring of vision (due probably to a paresis of accommodation). Either one or the other side-effect was seen, according to several correspondents, in 2 to 4% of all patients treated with chloroquine at full dosage. Pruritus seems to have been especially common in women, and was either general or localized in the perineal region or on hands and feet. Antihistamine drugs relieved this symptom, but in a few cases were without effect. Both these side-effects were temporary and abated within one week after the drug had been discontinued. Other minor complaints following

the administration of chloroquine were urticaria and oedema (4 cases), dizziness (8 cases), insomnia (3 cases), mental depression and abdominal discomfort (3 cases).

Amodiaquine.—Except for one case of vomiting, dizziness, and collapse in a child given 600 mg. of amodiaquine by mouth, no other side-effects were recorded, but the number of cases when this drug was used was small.

Proguanil and Pyrimethamine.—These are rarely used for treatment of malaria, and most of the side-effects reported were connected with the prophylactic regimen. Only 13 medical officers noticed any side-effects of proguanil taken in daily dosage of 100–200 mg. Most of these symptoms consisted of abdominal discomfort, diarrhoea, anorexia; there were, however, five cases in which proguanil was apparently causing stomatitis and mouth ulcers in adults, two cases of haematuria in children after an administration of 200 mg. of the drug, and one case of dermatitis resembling erythema nodosum. No side-effects were reported following the administration of *pyrimethamine* at standard doses, but there were seven cases of acute accidental poisoning of children. Five of these (four in European children and one in an African) proved to be fatal. The history of most of these cases was essentially the same: a child between 2 and 5 years of age found a bottle of pyrimethamine tablets and swallowed a number (15–25) of them. Within 30 minutes to 2 hours the child developed convulsions, occasionally vomited, collapsed, and either died one to three hours later or recovered. In two of these cases prompt medical action saved the child. In one case pyrimethamine could not be incriminated with any certainty. Apart from acute poisoning there were five cases of chronic toxicity of pyrimethamine given to one infant and four children at gross overdosage—for example, three tablets a week for six weeks or one tablet daily for three weeks). This was followed by asthenia, severe megaloblastic anaemia, and, in the case of two African children, death from a condition diagnosed tentatively as agranulocytosis.

Although the medical questionary brought some evidence of the type and frequency of side-effects in regular takers of antimalarial drugs for prophylaxis it was thought that more direct information could be obtained from the large residential group in Lagos. A few specific points in the questionary designed for the lay public called for definite answers which could be of value in this investigation.

As it was well known that some people keep changing their antimalarial prophylactic drug while others are faithful to one for a long time, an appropriate point calling for a reply was inserted in the questionary addressed to the residents in Lagos. The results are shown in Tables VI and VII.

A total of 527 residents of Lagos stated that they had changed at one time from one drug to another. This change was more frequent among adults (29%) than among children (17.5%) or infants (15%), with no significant difference between sexes.

Of all people changing drugs, the greatest number (279) changed from proguanil, forming 52.9% of those who changed drugs and 13.8% of the total in this survey; 75.6% of these went over to pyrimethamine—more children (87.0%) and infants (85.7%) than adults (72.5%). Chloroquine was the next most popular choice (55 persons, 19.7%). Mepacrine and quinine—the two "old-fashioned" drugs—were both abandoned by 19.5% of those who changed. Of those who stopped mepacrine, 75.7% went on to proguanil and 11.7% to pyrimethamine. Of the erstwhile quinine-takers, 68.9% preferred proguanil and 21.4% pyrimethamine. People who took chloroquine and pyrimethamine *ab initio* seem to be well satisfied with these drugs, changes occurring in only about 1% of the series.

The reason for a change of drug was also asked for. The answers were tabulated under the following headings: "Not effective," "personal preference or other reasons," "ill effects" (Table VII). Noticeable is the number of persons who abandoned proguanil from personal preference—mostly for pyrimethamine, on account of the convenience of a weekly dose as opposed to a daily one, particularly in children. Nevertheless it is worth remarking that some people gave the contrary reason for changing from pyrimethamine to proguanil, because they found the daily dose easier to remember than the weekly one. As regards the incidence of ill effects, there were no significant differences between the various drugs, except in the case of mepacrine, which always was notoriously unpopular because it stained the skin yellow.

TABLE VII.—*Reasons for Changing Antimalarial Drugs in Lagos, 1956*

Drug Changed from	Reason for Changing						Total	
	Not Effective		Personal Preference		Ill Effects			
	No.	%	No.	%	No.	%	No.	%
Proguanil ..	52	18·6	114	40·9	113	40·5	279	100
Chloroquine ..	3	13·0	9	39·1	11	47·8	23	100
Pyrimethamine	6	31·6	1	5·3	12	63·1	19	100
Mepacrine ..	31	30·1	—	—	72	69·9	103	100
Quinine	24	23·3	36	34·9	43	41·8	103	100
Total ..	116	22·0	160	30·4	251	47·6	527	100

Note.—The percentages refer to the relative proportions of the different reasons in the number of people changing from that particular drug.

Gastro-intestinal upset was the commonest ill effect attributed to any drug; the usual symptoms were anorexia and nausea, often accompanied by dyspepsia and flatulence. Pyrimethamine appears to be the least offensive in this respect. Headache, insomnia, depression, together with lassitude, forgetfulness, and irritability—a syndrome for long popularly recognized as "coast-head"—was attributed to a drug by 40 people (15.9%) complaining of ill effects; all stated or implied that their symptoms disappeared on changing their drug. As was to be expected, mepacrine was the principal cause of skin trouble, and quinine of symptoms referred to the ears; other complaints, often vague and unconvincing, accounted for 10% of "ill effects," fairly randomly divided between the various drugs.

(4) Consumption of Antimalarial Drugs in Nigeria

A brief reference to the consumption of antimalarial drugs in Nigeria was made in a previous paper (Bruce-Chwatt, 1951), but the changing trends in the demand for these drugs can be assessed best from total amounts issued by the medical departments stores every year. Table VIII quotes the total number of tablets (in thousands) of each of the five main antimalarials indented during the period

TABLE VI.—*Numbers of Residents in Lagos Changing Their Drug*

Drug Changed from	Drug Changed to													
	Proguanil		Chloroquine		Pyrimethamine		Mepacrine		Quinine		Amodiaquine		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Proguanil			55	10·4	211	40·0	6	1·1	6	1·1	1	0·2	279	52·9
Chloroquine	17	3·2			5	0·9	—	—	1	0·2	—	—	23	4·4
Pyrimethamine ..	10	1·9	8	1·5			—	—	—	—	1	0·2	19	3·6
Mepacrine	78	14·8	5	0·9	12	2·3			8	1·5	—	—	103	19·5
Quinine	71	13·5	8	1·5	22	4·2	2	0·4			—	—	103	19·5
Total ..	176	33·4	76	14·4	250	47·5	8	1·5	15	2·8	2	0·4	527	100·0

1952–7 by medical officers of the Federal and the three Regional Governments. It should be pointed out that this table does not show the straight consumption of antimalarials; during the past five years the number of hospitals and dispensaries opened in Nigeria had increased very considerably, and the figures in Table VIII reflect to some extent the ordering of new supplies for the greater number of treatment centres. Data concerning the consumption of drugs by private persons and commercial firms are not included in this table as they are not easily available.

Details of the consumption of parenteral preparations of antimalarial drugs are of less interest, but it might be added that the estimated number of ampoules of mepacrine (at 100 and 300 mg.) ordered by the governments in 1956 was 40,000, while the respective figure for quinine ampoules (at 6 and 10 gr. (400 and 650 mg.) was 30,000, and for ampoules of chloroquine 15,000.

The estimated cost to the governments of all antimalarial drugs used in 1956 for both prevention and treatment of malaria was approximately £60,000.

TABLE VIII.—*Amounts of Antimalarial Drugs in Tablet Form (in Thousands) Purchased by the Government Medical Departments in Nigeria During the Period* 1952–7

Year	Quinine Tablets (All Salts) at 5 gr. (650 mg.) Each	Mepacrine Tablets at 100 mg. Each	Chloroquine Tablets at 150 mg. Base Each	Proguanil Tablets at 100 mg. Each	Pyrimethamine Tablets at 25 mg. Each	Amodiaquine Tablets at 200 mg. Base Each
1952	636	12,089	—	5,000	—	—
1953	242	8,647	91	2,007	11	—
1954	155	9,350	368	3,278	44	—
1955	240	9,424	1,042	10,018	121	59
1956	171	10,153	1,831	8,466	213	168
1957 (Approx.)	92	10,291	3,115	8,522	701	376

DISCUSSION

Difficulties in the correct diagnosis of malaria mainly from clinical symptoms, with little help from the blood examination, are considerable in West Africa, and are responsible to some extent for the unreliable malaria morbidity statistics of Africans and Europeans in Nigeria.

Information obtained through two questionaries provided some new data on the incidence of malaria in the expatriate non-African population. It appears that the overall annual malaria morbidity of this population in the Federation of Nigeria fell from 225 per 1,000 in 1950 to 142 per 1,000 in 1956. Improvements in methods of malaria control in urban areas might have contributed to this gratifying decrease in morbidity, but the main cause of this is probably better individual protection and particularly the widespread use of more active prophylactic antimalarials. The disappearance of blackwater fever following the substitution of suppressive quinine by synthetic antimalarials is striking.

A survey of the therapeutic use of antimalarials in Nigeria revealed that as a whole the clinical medical practice in this country reflects creditably the remarkable advances achieved by experimental chemotherapy during the past ten years. Several interesting points were gathered from the answers to the medical questionary.

Chloroquine, given orally and parenterally, has become a drug of choice for the treatment of malaria in Nigeria. There can be little doubt that this drug is most effective and that the administration of the "loading dose," which averages two-thirds of the total dose, over three to five days is a correct procedure.

In spite of the popularity of chloroquine, quinine and mepacrine are still used; the former mainly for parenteral administration in severe malaria, the latter both by mouth and intramuscularly, somewhat indiscriminately, especially in rural areas.

The survey revealed a disturbing number of grave side-effects of intramuscular administration of mepacrine in infants and young children. This disadvantage has been known for some time, but the frequency of these often fatal incidents was underestimated, as they were not widely known. It might be argued that 29 fatal sequelae of the intramuscular injection of mepacrine in children constitute a small proportion of all cases in which this treatment was beneficial, but it should be remembered that the number of accidents quoted above is probably only a proportion of all cases.

Similar observations were made in East Africa a few years ago (Dockeray, 1951) and confirmed in Uganda by Trowell (personal communication) and by Luder (1957). One such case, of toxic mepacrine encephalopathy in a child given a mepacrine injection in the absence of malaria, was described by one of us (Bruce-Chwatt, 1955). The experience in Nigeria is not in agreement with that of Covell *et al.* (1955), who maintain that mepacrine convulsions are alarming but seem to have no serious effects.

It must be admitted that chloroquine is not entirely blameless in this respect, and the two cases of acute toxic effects of intramuscular chloroquine, quoted by our medical correspondents, are similar to those described in Ghana by Harris (1955). Nevertheless at the present time the general consensus of medical opinion is that intramuscular chloroquine is safe when properly administered. It is certain that the danger of parenteral administration of any antimalarial will be greatly decreased if the drug is given in two or three fractional doses, over one to one and a half hours. Attention should be drawn to the importance of calculating the dosage of intramuscular chloroquine in relation to the actual weight of children and not by a rule of thumb referring only to the age of the child (Harris, 1957). Oral administration should be preferred whenever feasible.

Serious side-effects after chloroquine given by the mouth were uncommon; on a full therapeutic dose of about 2 g. over four to five days pruritus and temporary blurring of vision might be quite troublesome in about 1% of patients. Amodiaquine has gained some favour among the medical profession in spite of the fact that there is no evidence that it is superior to chloroquine. A comparative study of the schizontocidal effect of both drugs (Charles, 1958) confirmed Davey's (1955) opinion "that amodiaquine cannot be used in any way—that is, in any particular dosage regimen—which is significantly different from a way in which chloroquine might be used."

The results of the medical questionary were of interest with regard to some important points mentioned by Covell *et al.* (1955). (1) Dosage of antimalarial drugs necessary for treatment of malaria in semi-immunes was about one-third to a half of that needed for the non-immune subject, and a short treatment consisting of 600 mg. of chloroquine in a single dose or 800 mg. of mepacrine over two days was usually effective. Good effects were also reported by those who used single-dose treatment of 600 mg. of amodiaquine. (2) There was no evidence of any strain of *Plasmodium falciparum* in Nigeria being resistant to therapeutic doses of chloroquine, mepacrine, or amodiaquine. However, some indirect and inconclusive reports have been quoted of increased tolerance by malaria parasites of proguanil or pyrimethamine given as suppressives. (3) There were justified complaints of the ever-increasing confusion created by the profusion of various proprietary names for the same active drug and by the varying dosages expressed either as a salt or as a base. Need was expressed for a reliable active drug without a bitter taste, suitable for paediatric practice.

With regard to the latter point, attention might be drawn to the recent confirmation by Clyde and Shute (1958), in Tanganyika, of the failure of the chloroquine methylene-β-hydroxynaphthoate reported by Bruce-Chwatt and Charles (1957).

Respective Values of Suppressives

When it comes to discussing the recent trends in the choice of suppressive antimalarials and their respective

values the conclusions deriving from the two questionaries are on less objective grounds. The use of antimalarial drugs for individual protection has been almost general in the expatriate population of West Africa for the past 50 years.* All senior Government officials and most of the senior staff in commercial undertakings, missions, etc., are supplied with antimalarials free of charge. A few years ago only quinine, mepacrine, or proguanil could be obtained on demand, but nowadays this extends also to chloroquine and pyrimethamine. Since the taking of an antimalarial is a normal feature of everyday life no wonder that the discussion of favourite antimalarial drugs is a popular conversational topic at any social gathering in Nigeria. There are unfathomable "fashions" in drug-taking, and many more or less imaginary complaints connected with them tend to obscure the real incidence of specific side-effects. All this, stimulated by an increasing amount of advertising, has led to an undesirable situation, as many expatriates are experimenting on themselves, using one or several drugs, often at dangerously high dosages.

It appears from replies to both the medical and the "residential" questionary that proguanil is taken by nearly three-quarters of all expatriates and by an increasing number of educated Nigerians. Pyrimethamine and chloroquine are the next choice, with amodiaquine third. In comparing these findings with those of the 1950 questionary the remarkable though expected trend is the eclipse of quinine and mepacrine as protective drugs. The other interesting fact is the generally increased dosage of proguanil as compared with the modal dose in 1950.

The changing trend in prophylactic antimalarials taken by a representative sample of the expatriate population of Nigeria can be seen best from the comparative figures obtained successively by the Bruce-Chwatts (1950), Nicol (1953), and the present survey.

The percentages of expatriates taking one or the other prophylactic antimalarial were as follows:

	1950	1952	1956
Proguanil	65%	68%	70%
Quinine	23%	16%	3%
Mepacrine	10%	6%	0·6%
Chloroquine	1%	2%	5%
Pyrimethamine			20%

General Protection

The true comparative value of the main drugs for the "general protection," in the sense given to this term by Covell *et al.* (1955)—that is, suppression of clinical symptoms, suppressive cure of *P. falciparum*, and causal prophylaxis—cannot be established from replies given to the two questionaries. Every drug, at whatever dosage taken, was alleged to have failed in approximately 6% of takers. This figure is in reasonably good agreement with the results obtained by Nicol (1953), who gave the percentage of "break-throughs" as 10.

Whether these break-throughs are genuine and due to the irregularity of drug-taking, or its underdosage, or an intercurrent gastro-intestinal illness interfering with the absorption of the drug, or unusually great exposure to infection, the presence of a resistant strain of the malaria parasite or other unknown factors is impossible to tell, though the first suspicion is justified and the following two causes are most likely. The possibility of relapsing infections with *P. malariae* or *P. ovale* of local origin cannot be dismissed, but is likely only in sporadic cases and not in nearly 10%. *P. vivax*, usually responsible for relapses of malaria, is so extremely rare in Nigeria that one or two imported cases would not account for more than a fraction of the incidence of malaria quoted above.

There is no factual evidence that proguanil- and pyrimethamine-resistant strains of *P. falciparum* might be responsible for some of the "break-throughs." A few personal comments of medical officers who had experienced an attack of malaria (with a positive blood slide) while on proguanil or pyrimethamine prophylaxis are insufficient to support this presumption. The incidence of malaria in regular takers of antimalarials generally and proguanil and pyrimethamine in particular has not increased in comparison with 1950, and it can be safely said that for the time being no drastic changes in the choice of suppressive drugs in Nigeria are necessary (Nigeria, 1949–54).

In Nigeria there has been an obvious trend to substitute pyrimethamine for proguanil, especially in children. The main, and good, arguments in favour of pyrimethamine are the lack of taste and the ease of giving a tablet once a week (usually on Sunday) instead of every day. It is of interest that in several replies to the questionaries correspondents admitted that they reverted to the daily proguanil regimen, as they found it difficult to remember to take pyrimethamine on only one particular day of the week and felt that the daily routine left much less margin for any possible errors of individual prophylaxis. On the other hand, the use of pyrimethamine once a week was most convenient in hospitals, schools, labour camps, antenatal clinics, etc., whenever a collective prophylaxis is carried out in a reasonably stable or supervised group. The problem of the best routine of prophylactic drug-taking is far from simple and must "take into account economics, human desires, and human failings" (Davey, 1955). This is of considerable importance with regard to the routine administration of prophylactic chloroquine, which is usually given twice a week at 300 mg. base; it is probable that a daily routine of 50–75 mg. would be a far better choice for individual prophylaxis.

It is of interest, therefore, that Davey and Robertson (1957) carried out a successful field trial of chemoprophylaxis with a daily dose of 50 mg. of chloroquine base because the daily regimen has been favoured by the Army authorities. Several years ago French workers adopted the daily prophylactic dosage of 100 mg. of chloroquine base, and since 1953 this method has been used throughout French West and Equatorial Africa with considerable success.

It will thus be understandable why the method of individual prophylaxis by amodiaquine—two tablets twice a month—is quite unrealistic and of doubtful value.

There is little evidence that any of the three commonly used prophylactic drugs (proguanil, chloroquine, pyrimethamine) produce any serious and consistent side-effects when taken at standard dosage. Pyrimethamine is probably the least responsible for any gastro-intestinal or other complaints commonly referred to other drugs. It is therefore all the more regrettable that during 1956 there were five fatal cases of poisoning due to pyrimethamine left within the reach of toddlers, attracted by the small size of the tablets and their lack of bitter taste.

All these cases are much the same as those of accidental pyrimethamine poisoning in children described by Taylor (1953), Davidson (1954), Gunther (1954), Peake (1954), Abbott (1955), Davies (1956), and in the Belgian Congo by Montauban *et al.* (1956), whose paper contains the best clinical description of acute pyrimethamine poisoning.

It should be added, in all fairness to the drug, that these accidents happened in Nigeria in 1956, before the introduction of the modern plastic strip pack of pyrimethamine, which should effectively prevent children from swallowing more than one or two tablets.

Five cases of long-term toxicity of pyrimethamine (megaloblastic type of anaemia), given at doses far in excess of those normally used, were more serious, as they were due to an error of judgment of the medical practitioner or to irresponsible self-medication by laymen. The main cause

*It is generally believed that the regular use of prophylactic quinine was introduced into West Africa in 1835. According to the late G. M. Findlay (*in litt.*), however, the "preventive quinine" was initiated on the West Coast in 1772 by Robert Robertson, a naval surgeon and a friend of James Lind, the promoter of the administration of "the bark for the cure of ague" in India. Robertson later became a Fellow of the Royal Society.

of the medical errors of judgment was the lack of appreciation of the differences between proguanil (which has a wide margin of safety) and pyrimethamine, remarkably active in small doses but toxic when given to children at several times its standard dose.

It appears that the conclusions of Myatt *et al.* (1953) about the reversibility of megaloblastic anaemia of adult volunteers on 25 mg. of pyrimethamine daily for several weeks do not necessarily apply to the blood-forming organs of children. The Federal Government of Nigeria, justifiably alarmed at the excessive dosage of pyrimethamine used in 1956 by some medical practitioners and by the lay public, circularized at the end of that year a warning to the medical profession in Nigeria. It appears that this warning was duly heeded, as only one case of overdosage of pyrimethamine came to light during the past year.

The replies to the medical questionary showed that there is a considerable measure of disagreement between medical practitioners in Nigeria regarding the value of drug prophylaxis in the indigenous population. The fact that out of 146 replies 100 did not express any definite opinion on this controversial subject indicates the gap in our knowledge of the problem of malaria immunity and its relationship with individual or collective chemotherapy. In view of the absence of a concerted opinion of the medical profession in Nigeria on the value of drug prophylaxis in the African population we express our own point of view.

In discussing the value of protective drugs in the indigenous population three groups of people must be distinguished. The first is a small but growing group of African infants and children either born in Europe or having been away for a long time and who are returning to the malarious areas. These should be treated, especially for some time after their return, as non-immunes and protected by the same drug regimen. The second group is constituted by antenatal clinics, infant welfare centres, schools, labour camps, etc. Such groups can be supervised; and here the value of antimalarial drugs is considerable, since they reduce the amount of sickness and decrease the infectivity of the human reservoir of infection.

An ideal drug in these conditions should have a combined curative and long protective action similar to that shown by pentamidine for prevention of trypanosomiasis. Unfortunately there is no such antimalarial at present, and all known drugs are excreted rapidly and have a short "carry over" value, so that a once-weekly or, at least, once-monthly administration is necessary whenever a long-term effect is sought. The choice lies between proguanil and pyrimethamine on the one hand and mepacrine, chloroquine, and amodiaquine on the other.

The first two have the advantage of low toxicity, low cost, and a potent sporontocidal effect, but they may induce parasite resistance, especially when used for treatment as well as prevention of malaria.

Chloroquine and amodiaquine are excellent for both purposes; their cost is still relatively high. Mepacrine has the advantage of being cheap, but it has several undesirable side-effects. The general consensus of opinion is still rather in favour of proguanil and pyrimethamine, but it is possible that in the long run chloroquine or amodiaquine will be the best in conditions where protection from malaria must start with its cure and especially where resistance to the first two drugs had appeared.

An indigenous child continuously exposed to malarial infection need not be given a continuous uninterrupted protective regimen from its early infancy through its whole life. There is no doubt that the administration to these children of adequate doses of active antimalarial drugs, particularly at the peak of the transmission season, will help the growing organism by easing the load of heavy parasitaemia without thereby hampering the progressive building up of the individual acquired immunity to malaria.

In the third group of the indigenous, large, and scattered rural population mass distribution of antimalarials could hardly achieve any permanent results (Bruce-Chwatt, 1956). Moreover, administrative difficulties of such mass distribution are enormous, and with the exception of some special circumstances, such as stopping an epidemic, the prevention of malaria by residual insecticides remains the only possibility, though mass treatment will speed up the interruption of transmission.

SUMMARY

Reliable data on the incidence of malaria are difficult to obtain in Nigeria, and the reported figures do not reflect the true situation.

The malaria morbidity of the expatriate population in Nigeria, which was estimated in 1950 at 225 per 1,000, had decreased in 1956 to 142 per 1,000. In an expatriate population of nearly 18,000 there was one death due to malaria and one to blackwater fever.

Information on antimalarial drugs obtained from two questionaries showed that chloroquine is the most popular therapeutic drug, with mepacrine second, and amodiaquine third. For severe malaria, quinine injections are still frequently used.

As a protective drug proguanil was the most favoured, followed by pyrimethamine and chloroquine. In about 6% of takers of all protective drugs "break-throughs" of malaria were reported, but the reasons for these break-throughs, as well as their diagnosis, are uncertain.

Intramuscular injections of mepacrine in infants and small children may be followed by serious and often fatal sequelae. Both mepacrine and chloroquine given at a full therapeutic dose may produce a number of side-effects which are usually transient. Side-effects due to protective drugs are rare, though in 1956 there were several cases of accidental fatal poisoning of children by pyrimethamine.

An assessment has been made of the amount of antimalarial drugs consumed in Nigeria in 1956.

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MALARIA AND PREMATURITY IN THE WESTERN REGION OF NIGERIA

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The amount of information available in tropical Africa on the relationship between malaria infection and prematurity is still inadequate. An investigation based on nearly 400 single deliveries is of sufficient interest to warrant this preliminary note.

The Wesley Guild Hospital, where this work was carried out, is a Methodist Mission Hospital which has been established in Ilesha (a town of about 80,000 inhabitants) for 45 years. During 1956 there were almost 12,000 attendances of 2,683 patients at the antenatal clinics and 815 deliveries in the hospital. Not all of these deliveries were from our own clinics; a proportion of these patients were women coming in from the surrounding villages to be delivered, and some were referred from local clinics.

The major problem facing any worker on prematurity in Nigeria is to determine whether an infant is premature or not. The W.H.O. (1950) has defined a premature baby as one which weighs less than 5½ lb. (2,500 g.) at birth, but this standard is not universally accepted for Negro children. The average birth weight of infants born in the Wesley Guild Hospital is between 6 and 6½ lb. (2,720 and 2,950 g.), which is much below the average of 7 lb. (3,180 g.) for England. Most of the African women who attend the antenatal clinics have no record of the last menstrual period, and no accurate estimation of the maturity of the infant can be made on the duration of pregnancy.

Present Investigation

Relationship between the malaria infection of the placenta and the weight of the child at birth was investigated on 392 single deliveries. The above sample had to be selected so as to exclude women who had taken any antimalarial drugs during the late months of the pregnancy. Quinine, mepacrine, and other drugs are readily obtainable in the local market, and a number of women take the drugs during pregnancy for "fever" or for various real or imaginary ailments or as a "tonic."

Immediately after the delivery of the placenta a wedge-shaped piece of it was cut from the maternal aspect of the organ and a smear was made on a slide. The film was fixed with absolute methyl alcohol and stained for 45 minutes in 5% Giemsa diluted in buffered water at *p*H 7.2. All the films were first examined by the technician and then rechecked without reference to the clinical data. The infants were weighed as soon as possible after delivery, usually within two hours of birth. The results are shown in Table I. The weights of newborn babies were classified into four groups, and the numbers in each of these groups in relation to the infection of the placenta are shown in Table II.

Adopting the term "premature" for all babies weighing less than 5½ lb. (2,500 g.) at birth, with the reservation that not all such Nigerian babies are necessarily premature, the percentage of premature babies is 37 in the infected group and 12 in the non-infected. The difference of 25% is 3.4 times its standard error and therefore statistically significant.

TABLE I.—*Relationship Between the Malaria Infection of the Placenta and Birth Weight*

	No.	%	Mean Birth Weight
Infected placenta	130	33	5 lb. 12 oz. (2,610 g.)
Non-infected placenta	262	67	6 lb. 7 oz. (2,920 g.)
Total ..	392	100	6 lb. 3 oz. (2,807 g.)

TABLE II.—*Four Groups of Weights of African Newborn in Relation to the Infection of Their Placenta*

Weights of Infants	Infected Placenta		Non-infected Placenta	
	No.	%	No.	%
Up to 3 lb. 4 oz. (1,474 g.)	2	1·5	—	—
3 lb. 5 oz. to 5 lb. 8 oz. (1,500 to 2,495 g.) ..	46	35·4	32	12·2
5 lb. 9 oz. to 7 lb. 12 oz. (2,523 to 3,515 g.) ..	76	58·5	215	82·1
More than 7 lb. 12 oz. (3,515 g.)	6	4·6	15	5·7
Total ..	130	100·0	262	100·0

It was thought to be of interest to analyse the proportion of infected placentae in relation to the parity of the mother, and the results of this investigation are shown in Table III, where all newborn babies below 5½ lb. (2,500 g.) are counted as premature.

TABLE III.—*Relationship Between the Parity of the Mother, Frequency of Placental Infection, and Birth Weight*

Para	Infected Placentae			Non-infected Placentae			Positive Placentae (%)
	No.	Premature		No.	Premature		
		No.	%		No.	%	
1	75	33	44·0	45	12	26·6	62·5
2	22	9	41·0	41	4	9·7	35·0
3	13	2	15·4	51	5	9·8	20·3
4	7	1	14·3	42	5	11·9	14·3
5	4	1	25·0	40	1	2·5	9·1
6 and over	9	2	22·2	43	5	11·6	13·5
Total ..	130	48	37·0	262	32	12·2	33·0

Of the infants born of the infected placentae, nine died in the first week of life (6.9%), but in the non-infected group only 3.4% died in the first week. These figures are in general agreement with the frequency of prematurity in each group.

In view of the interest in the problem of sickling and malaria infection (Livingstone, 1957), 306 mothers were tested for the presence of the sickle-cell trait, using 2% sodium metabisulphite solution mixed with a drop of blood under a sealed coverslip.

The overall sickling rate in 306 mothers was found to be 10%; the sickling rate of 100 women with infected placentae was 11%, and the corresponding rate in 206 women with non-infected placentae was 9.2%. The difference of 1.8 is less than twice its standard error, and this would suggest that sickling has little effect on the development of the malarial parasite in the placenta.

The problem of congenital malaria in Nigeria has recently been discussed (Atkins, 1957; Bruce-Chwatt, 1957), and the opinions expressed were quite contradictory. In an attempt to obtain some data from Western Nigeria 117 newborn babies were investigated for the presence of malaria parasites in their peripheral blood within 24 hours after birth. The corresponding placentae were also examined. It was found that 30 placentae were infected with malaria parasites, giving a percentage of 25.6. None of the 117 newborn were found to be infected.

Discussion

Prematurity is the commonest cause of neonatal death, and it has been suggested that malarial infection of the mother, and consequently the placenta, is one of the causes of prematurity in Nigeria. Bruce-Chwatt (1952) examined the placentae of 310 single deliveries in Lagos and its vicinity, and showed that 73 (23.6%) were positive, and that the average birth weight of babies born with these placentae was 145 g. (4 oz.) less than the average birth weight of those born with non-infected placentae. Archibald (1956), working at Ilaro in the Western Region of Nigeria, found malarious placentae in 77 cases (15%) out of a series of 463; the average birth weight of babies from infected placentae

was 6 lb. (2,720 g.), and from non-infected placentae 6 lb. 6 oz. (2,890 g.), a difference of 6 oz. (170 g.).

The present investigation confirmed these findings and showed that 130 African babies whose placenta was infected with malaria parasites had a lower mean birth weight than 262 whose placenta was not infected. The difference in birth weight between the two groups was 11 oz. (312 g.). The proportion of newborn with very low birth weights was greater in those whose placenta was infected.

It appeared that there is a negative correlation between frequency of infection of the placenta and the parity of the mother. The increasing resistance to the infection might be due simply to the increasing average age of the women at each successive parity and correspondingly higher degree of immunity. It is of interest, however, that the percentage of babies weighing less than 5½ lb. (2,500 g.) is increased in the malarious group at each parity. The comparison between the average birth weights and percentage of prematurity of South African babies of various races (Salber and Bradshaw, 1953) with Nigerian babies born in Ilesha is of interest. It will be seen from Table IV that the average birth weight of Nigerian infants is lower, and the percentage weighing less than 5½ lb. (2,500 g.) at birth higher than any of the four races, including the Bantu, which are of negro stock.

TABLE IV.—*Birth Weights of South African Babies Compared with Nigerian Babies*

Race	Average Birth Weight	Percentage Less Than 5½ lb. (2,500 g.)
European S.A.	7 lb. 8 oz. (3,400 g.)	4·2
Coloured S.A.	6 lb. 14 oz. (3,120 g.)	9·6
Bantu S.A.	6 lb. 12 oz. (3,060 g.)	11·5
Indian S.A.	6 lb. 7 oz. (2,920 g.)	18·3
Nigerian (Ilesha)	6 lb. 3 oz. (2,805 g.)	20·4

An investigation of the presence of congenital malaria in a sample of 117 newborn babies showed that, although 25.6% of them had infected placentae, no malaria parasites could be found within 24 hours after birth in any newborn infant. This confirms the results obtained by Bruce-Chwatt (1952) and indicates that congenital malaria is very rare in the indigenous population of Nigeria, in spite of the frequent infection of the placenta.

Summary

Out of 362 newborn African babies 30% had a placenta infected with malaria parasites.

The mean birth weight in the 130 newborn that had an infected placenta was 11 oz. (312 g.) less than the birth weight of 262 whose placenta was not infected.

There were 33% of premature babies in deliveries where the placenta was found infected with malaria parasites; in deliveries with non-infected placenta the respective figure was 12%.

There was no case of congenital malaria among 117 newborn, 25.6% of whom had an infected placenta. There appears to be a negative correlation between frequency of infection of the placenta and the parity of the African mother.

I thank Dr. C. A. Pearson, medical superintendent, Wesley Guild Hospital, Ilesha, for his co-operation. I am grateful to Dr. L. J. Bruce-Chwatt, Federal Malaria Service, Medical Department, Lagos, for his help and guidance; to Dr. D. C. Morley for his assistance; to Mr. Ladele and Mr. Fasuyi for laboratory and clerical work; and to Miss Lethbridge and staff of the maternity unit for their co-operation.

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MECHANISM OF ACUTE HYPOTENSION FROM FEAR OR NAUSEA

BY

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It is common knowledge that emotion, particularly fear, may cause syncope. There are great difficulties, however, in obtaining records of the circulatory events which precede the attack, and many situations, such as high-flying jet aircraft or the altar steps, are impossible to investigate.

There is a small amount of evidence that the final mechanism of syncope induced by fear of needles is the same as syncope induced by haemorrhage, for Brigden *et al.* (1950) and Greenfield (1951) each demonstrated vasodilatation of forearm vessels in a single subject during the phase of low blood pressure.

Further evidence has now become available. An investigation into the cause of cerebral damage following nitrous oxide anaesthesia for extraction of teeth was suggested by the clinical material collected by Bourne (1957). It was at first thought that reduction in arterial oxygen saturation might be the main factor, but it is shown in this paper that severe hypotension is not uncommon, and that a precipitating cause is the well-known fear of the dental chair.

Emotion is often associated with nausea, and either or both may cause syncope. The effects of spontaneous nausea have from time to time been recorded in this laboratory during the course of circulatory observations, and the treatment of alcoholic patients with apomorphine allowed an opportunity of obtaining control records before nausea was induced.

Material and Methods

The subjects were volunteers; the dental patients being young healthy males (21 to 39 years) in need of urgent extraction of one or, at the most, two teeth. The alcoholic patients were older males (40 to 60 years).

Intravascular and intrathoracic pressures were measured with capacitance manometers and changes in arterial oxygen saturation with a continuously recording photoelectric device on the ear. Forearm flow was measured by venous occlusion plethysmography and recorded on the same photographic paper as the measurements of vascular pressure. Plethysmography was unsuitable in the dental cases owing to the inevitable final phase of violent muscular movements. In some subjects, however, the vascular resistance of a limb was measured by an arterial "run-off" method (Hayter and Sharpey-Schafer, 1958). In this method the artery is suddenly occluded by a high-pressure cuff. The rate of fall of arterial pressure distal to the cuff varies with the vascular resistance in the limb. This resistance, calculated by an empirical method, shows a good correlation with the resistance calculated from simultaneous pressure and flow measurements. The method is rapid, as only 2 seconds' occlusion is necessary for calculation, and is relatively free from artifact when violent muscular movements are to be expected.

Results

Effects of Dental Gas

Twenty-one subjects were investigated, five developing hypotension and the remainder showing evidence of the effects of emotional stress on the circulation. Circulatory

Data From Continuous Records Just Before Administration of N_2O

Case No.	Heart Rate	Pulse Pressure (mm. Hg)	Arterial Pressure (mm. Hg)
1	108	80	152/72
2	105	96	191/95
3	143	68	145/77
4	111	100	201/101
5	135	85	175/90
6	92	50	134/84
7	98	68	151/83
8	102	84	174/90
9	109	108	201/93
10	96	75	161/86
11	112	67	135/68
12	96	95	195/100
13	115	72	158/86
14	90	43	115/72
15	94	66	126/60
16	112	60	126/66

data obtained from continuous arterial records just before administration of N_2O are shown in the Table. In many subjects both heart rate and pulse pressure were considerably increased.

On giving gas the mean arterial pressure and pulse pressure increased still further and the arterial oxygen saturation fell to about 60% (Fig. 1). With tooth extraction or severe asphyxia large changes in intrathoracic pressure were superimposed on the arterial pressure trace, while in some subjects violent pronation of the forearm interfered with recording in the brachial artery. During induction of anaesthesia the arterial "run-off" method showed constriction in the forearm.

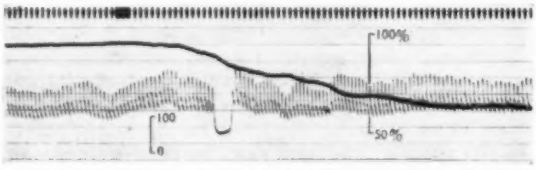

FIG. 1.—Upper trace: arterial O_2 saturation. Lower trace: arterial pressure. N_2O was given at the black signal on the time marker. Calibrations in mm. Hg, % saturation, and time marker in seconds in this and subsequent figures.

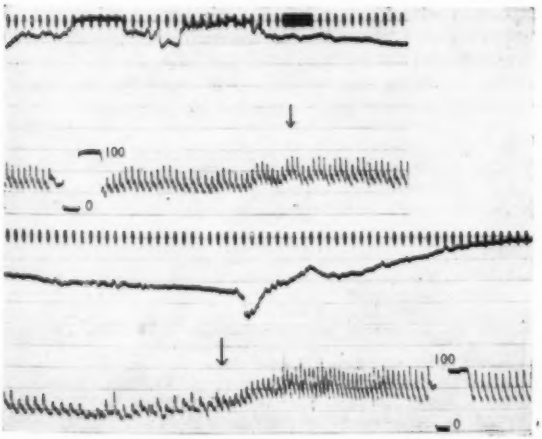

FIG. 2.—Upper trace: arterial O_2 saturation. Lower trace: arterial pressure. N_2O was given at the first arrow and the subject tipped into the supine posture at the second arrow. Arterial pressure was low before the anaesthetic was given. There is a gap of 15 seconds between the upper and the lower record.

Administration of N_2O was not the main factor in causing hypotension, since in four out of five subjects arterial pressure was low before the mask had been placed on the face (Fig. 2). Indeed, in two subjects the giving of gas raised the previously low blood pressure. One subject had hypotension and syncope when tipped into the erect sitting posture preparatory to proceeding with the dental gas, recovered when tipped into the supine position, again had syncope when erect, and was finally successfully anaesthetized and a tooth extracted while supine.

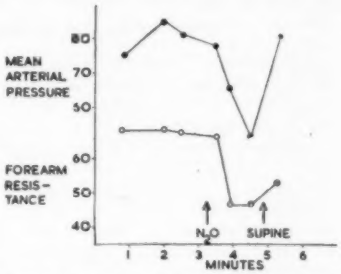

FIG. 3.—Data calculated from a continuous arterial record. Forearm resistance was measured by an arterial run-off method (Hayter and Sharpey-Schafer, 1958). With the fall in arterial pressure there is vasodilatation in the forearm. Arterial pressure in mm. Hg and forearm resistance in arbitrary units.

The final, or efferent, mechanism of the fall in arterial pressure is shown in Fig. 3. The vasodilatation in forearm vessels was similar to that found in syncope induced by haemorrhage (Barcroft *et al.*, 1944) or by fear of needles (Brigden *et al.*, 1950). Bradycardia was also present and pallor of the skin persisted afterwards for many minutes, suggesting discharge of posterior pituitary hormone.

There remains the problem of how this vasovagal fainting reflex is initiated. The evidence presented above suggests that emotion or fear is the main factor. Reduction in arterial oxygen saturation, which can also result in vasovagal fainting (Anderson *et al.*, 1946), would seem to be only a possible additional cause.

Effects of Apomorphine

Five alcoholic patients were investigated in the supine position. Effective right auricular pressure (right auricular pressure minus intrathoracic pressure) was measured by the differential manometer system described by Lee *et al.* (1954). Arterial pressure and forearm flow were recorded on the same photographic paper. After a control period a suitable alcoholic drink was made available and 4 mg. of apomorphine was given intramuscularly. Some minutes later, when nausea and yawning appeared, effective right auricular pressure fell (3 to 7 mm. Hg), the heart rate increased, but the mean arterial pressure was maintained. Still later, in three subjects, the mean arterial pressure fell below 50 mm. Hg and there was bradycardia and vasodilatation of forearm vessels (Fig. 4).

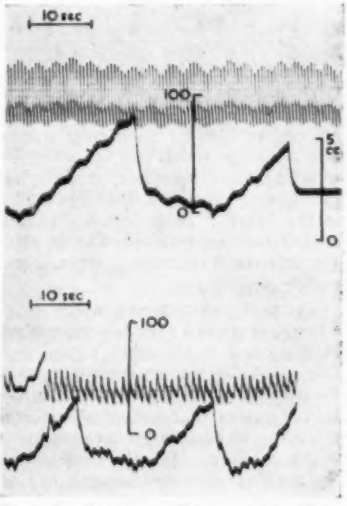

FIG. 4.—Syncope after apomorphine. Upper trace: arterial pressure. Lower trace: forearm volume. The rate of rise of volume on applying a collecting pressure is proportional to the flow. Upper record: before apomorphine. Lower record: after apomorphine, showing hypotension, bradycardia, and dilatation of forearm vessels.

About 30 other cases of spontaneous nausea have been observed, in which right auricular pressure fell with the onset of nausea. Differential manometer systems were not used in these cases, so that possible changes in intrathoracic pressure were not taken into account. The evidence suggests that dilatation of the peripheral venous system precedes hypotension in syncope induced by nausea.

Effects of Emotion in Heart Failure

The vasovagal fainting reflex has not been recorded in patients with heart failure. Such cases have been bled up to 2,000 ml. without firing this reflex (Howarth *et al.*, 1946), while venesections of 1,000 ml. cause fainting in over 50% of normal subjects (Wallace and Sharpey-Schafer, 1941). Circulatory measurements of all kinds have been made by one of us in about 700 patients with heart failure. None fainted from emotion, nausea, or other cause. Any explanation, therefore, of the afferent mechanism of the faint reflex in normal subjects must take into consideration that it does not operate in heart failure.

Discussion

Emotional fainting might be mediated in a simple fashion from the central nervous system via the efferent vasomotor nerves, causing vasodilatation in muscle vessels. If this were so, there is no reason why subjects with heart failure should not faint; indeed, many of those with a low cardiac output might well develop hypotension more easily than normal subjects. So simple a mechanism, therefore, does not cover all the facts. The most attractive explanation at the present time is that there is an afferent pathway for this reflex fired from the heart itself and that diminution of the amount of blood and virtually complete emptying of a ventricular chamber during systole is the stimulus. (With a failing circulation ordinary procedures are unlikely to empty the heart completely and the faint reflex, therefore, is not brought into play.)

The results presented in this paper suggest that there are two ways in which emotion may tend to empty the heart in normal subjects. The first is by nervous stimulation of the contraction of the heart, initially increasing the stroke output; the second is reduction of filling pressure, possibly due to venodilatation in the splanchnic area. Stimulation of the contraction of the heart simultaneously with decreased filling pressure has been studied by Henry and Gauer (1950) in dogs. Following reduction in cardiac filling pressure by bleeding, they gave adrenaline and were able to show that large pressure transients developed during systole in the cavity of the left ventricle when that chamber was virtually emptied of blood. Such large transients might well stimulate receptors which are known to exist in cardiac muscle. It is suggested, therefore, that the effect of emotion is indirect, first causing a diminution of the amount of blood in the heart. Then impulses pass from the heart to the central nervous system. Thence the reflex is mediated via the efferent vasomotor nerves, causing vasodilatation of muscle vessels.

There are other events which support this theory. Recovery occurs in a very few seconds when the filling pressure of the heart is raised by tipping into the supine position (Fig. 2). Continuous records, too, may show conspicuous fluctuations of arterial pressure with respiration during the initial phases of fainting which suggest that reflex vasodilatation is occurring intermittently with small changes in filling pressure. Finally, there seems to be some truth in the popular belief that fainting may be prevented by "taking a grip of oneself," since muscular tensing, or movement, can cause the low arterial pressure to rise (Brigden *et al.*, 1950), presumably by increasing the amount of blood in the heart above the critical level. This last mechanism may explain the recovery that took place in some dental patients when nitrous oxide was given.

Effects of Forced Maintenance of an Upright Posture

Normally a person who faints falls to the ground and arterial pressure is restored in a few seconds. In the dental chair or the ejection seat of a jet aircraft the upright sitting posture is forcibly maintained, and arterial pressure can remain for many minutes below 40 mm. Hg at heart level. Of these two similar situations, the latter is clearly more dangerous. There is some evidence from pilots who have recovered and landed safely that a number of mechanisms may cause syncope. Fear and nausea, hyperventilation, coughing, and the Valsalva manœuvre have been described, while heat at over Mach 1 and the immobile sitting posture are additional factors. Of these mechanisms, fear and nausea might produce the longest period of hypotension, for, provided no mechanical disaster occurred to the aircraft, baroceptor constriction should restore consciousness in about 10 seconds in the others. A pressure suit is a complete answer to all these mechanisms, the difficulty being to blow it up when it is needed.

The dental chair is a simpler problem. Unfortunately our observations showed that the dental surgeon and anaesthetist did not recognize that severe hypotension was present and were apt to call this state "a nice quiet gas." They were clearly prepared to go on extracting teeth under relatively good conditions. Dental surgeons seem to be unwilling to extract teeth in the supine posture. They claim that their instruments are unsuitable, but it is more probable that they fear legal action should teeth or the effects of aspirated blood clot appear on an *x*-ray film of the chest. It is unlikely that the complete answer—extraction in the prone position—will be popular. At second best, patients might be pulled out of the chair on to their faces, on the floor, when palpation of the pulse suggests that severe hypotension is present.

Summary

Continuous circulatory measurements were made before and during N_2O anaesthesia for tooth extraction and the administration of apomorphine for chronic alcoholism. Five out of 21 dental patients developed acute hypotension with vasodilatation of forearm vessels, four of these before the anaesthetic was given. Fear appeared to be the main cause, with a fall in arterial oxygen saturation as a possible minor factor. Apomorphine-induced nausea caused a fall in the effective filling pressure of the heart which preceded hypotension and syncope.

It is suggested that emotional stimulation of the heart beat and a fall in cardiac filling pressure cause virtual emptying of a ventricular chamber during systole which fires the afferent mechanism of the faint reflex. There is strong evidence that subjects with heart failure, whose ventricles are not easily emptied, do not faint.

We are indebted to the anaesthetists and dental surgeons of St. Thomas's Hospital for their collaboration.

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SEX HORMONES AND MAMMARY CANCER

EXPERIENCE WITH DURABOLIN

BY

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Whilst the effect of hormones on the growth of cancer cells in general is still completely unknown, some relationship between sex hormones and cancer of the breast seems highly probable—a relationship that clearly is exceedingly complex. This is at once evident from the various ways in which a patient suffering from mammary cancer may react to sex hormone therapy. Ira T. Nathanson (1949) said: "The point which comes to my mind is that we may have two people of the same age, with the same tumour histologically, with the same physiologic characteristics, with the same mode of spread, who, to all intents and purposes, are metabolically identical; we give them hormones of the same kind, from the same bottle, on the same day; but one patient goes on to death in a short period of time and the other patient has a nice regression and goes on for a year and a half or two years before death."

The fact that of two mammary carcinomas of the same histological structure the one metastasizes in an entirely different way from the other suggests the existence of different kinds of breast cancer. The above-quoted statement concerning the experience that in spite of similar structure and metastases a different reaction to hormone therapy may occur shows that apparently there are various differences in the nature of these carcinomas which so far we have been unable to distinguish clearly by other means.

Statistics on the incidence of breast cancer in various age groups all show a kind of maximum in the climacteric, followed by a minimum and then a renewed increase. Pirquet (1930) inferred from this that there are two kinds of cancers—genital cancers and age cancers. I have recently (van der Werff, 1956) come to a somewhat different conclusion—that is, that two groups of breast cancer exist side by side: (1) oestrogen-dependent cancers which are stimulated by ovarian activity and can develop only in the reproductive period; and (2) age cancers which are independent of this ovarian activity and the disposition for which increases regularly with age (Fig. 1). This hypothesis explains why in some of the patients in the reproductive period oestrogen therapy results in a rapid exacerbation. In the menopause this seems to be not so, and sometimes oestrogens even have a favourable therapeutic effect.

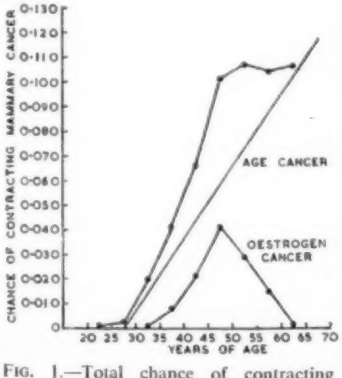

FIG. 1.—Total chance of contracting mammary cancer, being the sum of the chances of age cancer and oestrogen cancer.

As regards the androgens, they seldom seem to cause a rapid exacerbation, but have mostly either a clearly favourable, though merely palliative, effect or none at all. The favourable response is seen mainly after administration of the most commonly used androgen, testosterone propionate, to patients with bone metastases.

Consequently, whereas it may be said of oestrogens that, according to the nature of the cancer, they have a positive, a negative, or no immediate effect on the growth of the tumour, it is far less clear whether androgens in certain cases can have a direct inhibitory effect on tumour growth or whether there is an indirect inhibition by means of the protein- and calcium-sparing action of these hormones, connected with stimulation of the general defence reaction.

However, in recent years it has become clear that, after prolonged administration and even in cases which originally showed a favourable response, androgens also in the end may stimulate tumour growth. This escapes observation because the impression is gained that the preparation has ceased to have effect.

Conversion of Steroids

In fact, according to recent research, the body is capable of gradually and to an increased extent converting certain androgens into oestrogens. This has long been suspected, not only from the similarity in structure of the oestrogenic and androgenic steroids but also from the fact that androgen therapy produced an increase in oestrogen excretion. While at first one might think of another process in which the production of oestrogens could be the result of stimulation by the administered androgens, recently more direct evidence has been obtained of a biological conversion of C19 steroids into C18 steroids by making use of radioactive ^{14}C. For example, incubation of human ovarian tissue and testicular tissue from stallions with testosterone-4-^{14}C resulted in the formation of oestradiol-17β-^{14}C. Intravenous administration of the same labelled androgen to a pregnant mare gave rise to excretion of oestrone-^{14}C. Finally the direct conversion of $\triangle^4$-androstene, 3,17-dione-^{14}C into oestrogenic hormone could be demonstrated, for example, in the ovary, placenta, and adrenal (Meyer, 1955; Dorfman, 1956). It is clear, therefore, that for prolonged administration a steroid is needed which does not show this conversion and yet possesses the favourable properties of the androgens used for the treatment of mammary carcinoma. As already stated, it is not really known in precisely what way the androgen can favourably influence the carcinoma, but if we consider testosterone propionate we can say that the following properties are useful: (1) a pronounced protein-sparing effect; (2) an inhibitory effect on the decalcification process caused by the bone metastases and as a result a reduction in calcium excretion; and (3) an analgesic effect due to the action mentioned under (2). On the other hand, testosterone propionate has certain less desirable properties, the principal one being the virilizing action which becomes manifest in deepening of the voice and in beard growth.

Properties of Durabolin

Apparently the new compound, norandrostenolone phenylpropionate ("durabolin") compares favourably as regards all these properties with testosterone propionate, the first but until now the most important hormone for use in mammary carcinoma (Overbeek and de Visser, 1957). In the first place it seems that conversion in the body into oestrogen is not so easy or is perhaps even impossible, so that there is a possibility that far more prolonged administration is necessary (Meyer, 1955). In addition it has an anabolic effect 12 times more powerful than testosterone propionate, and the calcium excretion in patients with bone metastases can be greatly reduced after administration, while the virilizing effect is far less pronounced. The duration of action is long, so that weekly injections of 25 mg. are sufficient. The preparation is well tolerated, and patients who show a favourable response often begin to feel much better, acquire a good appetite, and look well. Although apparently conversion into oestrogen cannot be the cause, it has

unfortunately been found that in the case of durabolin the action wears off. From a certain moment the responsive patients also are seen to go slowly downhill and finally succumb.

Now, it is a significant fact that hormone therapy is almost exclusively instituted at an advanced stage, when the usual therapeutic measures have been exhausted and the patients show recurrences or generalized metastases, in which cases total recovery is no longer possible. It is feasible, therefore, that hormone therapy might have a curative effect if surgical and radiological treatments are immediately combined with the hormone therapy; but, on the other hand, in that case it will be very difficult to prove that this hormone therapy has been the decisive factor in the complete recovery. Without hormone therapy approximately one-third of the patients treated for cancer of the breast recover. A follow-up of a very large number treated in this way might produce the required evidence only after many years.

Results with Durabolin

The following results were obtained with durabolin in patients suffering from breast cancer. This group included 13 patients with such marked generalized metastases that recovery could not be expected. Eight of these have meanwhile died. In eight other patients the metastases were not yet very pronounced but other conditions made the prognosis very bad, and durabolin was administered to improve this. All are still alive.

In practically all 21 patients considerable improvement in the general condition was observed during weekly administration of 25 mg. of durabolin. This became manifest in alleviation of pain which was sometimes very severe as a result of bone metastases, in a good appetite which led to a considerable weight-gain, and in a general sense of well-being. This satisfactory condition, however, is often in complete contrast to the radiological findings. Although occasionally some slight calcification in bone metastases is observed, this is usually not clearly marked, and, in spite of a seemingly good general condition, the bones prove to be in a deplorable state.

In contrast to testosterone propionate, the durabolin is well tolerated for many months and the unpleasant symptoms of virilization occur only sporadically. The most striking of these is the inability to sing. Van Dommelen (1956) noticed that the administration of a single large dose of durabolin gave rise to such a severe calcium retention in the bones that there was a grave risk of hypocalcaemia and tetany. This was not so in any of the 21 patients, though the blood calcium usually fell slightly. In a number of cases the alkaline phosphatase was determined regularly. Here also varying reactions were found. In responsive cases in which this level was raised it fell fairly soon and continued to vary around a value which often was still too high. In one patient durabolin had no effect and the alkaline phosphatase continued to rise. When finally ethinyl-oestradiol ("lynoral") was given, this level fell critically. The case is discussed below. This patient belonged to the group of 13 of whom it was known beforehand that they could not be saved and of whom eight have died. Some of them, however, showed a dramatic improvement which, though of a temporary nature, was quite unexpected. Two of these cases are discussed in detail.

Case 1

A woman aged 43 had an operation in June, 1953, for carcinoma of the left breast and post-operative irradiation. In November she complained of "rheumatism" and stayed in bed for two months. Her doctor then treated her with testosterone phenylpropionate, and in March, 1954, she felt well and had gained 10 kg. in weight. However, gradually "shooting pains" began to occur again, and on January 1, 1955, having already given radiotherapy to the patient, I was called in for consultation and found her in a deplorable condition. She was suffering excruciating pains as a result of generalized bone metastases and vomited after administration of morphine or other potent analgesics. The vomiting could be stopped immediately by injections of chlorpromazine. The pain could then be relieved with analgesics and the patient could again take food, after which the general condition improved. This improvement continued for a considerable time, but in July she was again in a hopeless condition. There were widespread metastases throughout the skeletal system.

In August durabolin therapy was instituted, first 25 mg. in a fortnight, then 25 mg. weekly, and still later 50 mg. a week. In September she was already feeling much better. The pain had gone and morphine was no longer needed. There was only a certain feeling of stiffness in the back, which was not surprising considering that the skeletal system was riddled with metastases. The alkaline phosphatase level fell from 39 King–Armstrong units in September, 1955, to 19 in January, 1956, and then remained at that value. An increase in the durabolin dosage was of no avail (Fig. 2). In March, 1956, the pain suddenly became very severe again, and her condition gradually deteriorated. While about Christmas the patient had been so well that she could travel by train and stay with her relatives, she was now confined to bed, began to decline slowly, and died on July 21, 1956.

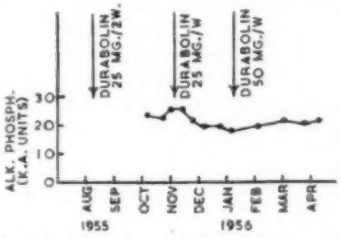

Fig. 2.—Case 1. Alkaline phosphatase during treatment with durabolin.

In the last few months durabolin was no longer tolerated. Virilization symptoms caused by durabolin were present only in a very slight degree.

Case 2

A woman aged 41 noticed a lump in the right breast in January, 1955, but did not go to the doctor until March, when there was also a lump in the axilla. The condition was complicated by a three-months pregnancy. She had an immediate operation, followed by irradiation, but in July there were supraclavicular nodules on the other side. Premature birth was induced and a healthy child was born.

On August 5, five days after parturition, large masses of nodules were observed in the neck. The neck was very painful, owing to a metastasis in C 2. There were also skin metastases around the vulva. Radiotherapy was given to the neck. Early in September the neck was still very painful but the nodules had disappeared. Unfortunately a tumour could now be felt in the left breast. Durabolin therapy was instituted, 25 mg. weekly. By the end of September the general condition had greatly improved. Only the tumour in the left breast was still present, but it had not grown larger. Mobility of the neck was much better. On October 11 her general condition was very good and the tumour in the left breast stationary.

Her general condition continued to be good. She could again do light housework and even ride her bicycle. She

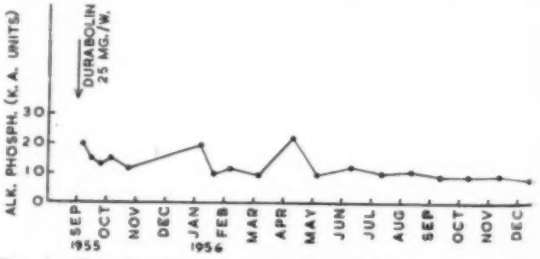

Fig. 3.—Case 2. Alkaline phosphatase during treatment with durabolin.

was troubled only by a repeatedly recurring erysipelas, which could be easily suppressed with sulphonamides and penicillin. In May, 1956, she was looking very well indeed and felt well. The tumour in the left breast was still present, but was smaller and mobile. An ablation now took place, which healed without difficulty. All this time the patient was given durabolin, one dose of 25 mg. a week. The alkaline phosphatase level, which in September, 1955, was 20 K.A. units, had fallen, and in December, 1956, it was normal (Fig. 3). Unfortunately in January, 1957, her condition began to worsen and ascites developed. Durabolin began to lose its effect, and in late February it seemed as if the end was near. In connexion with an article by Goldsborough (1957) a course of chorionic gonadotrophin treatment was given (500 units three times a week). It has been reported that the patient is beginning to improve once more. She was still alive in April, 1957.

Case 3

This case, referred to above, shows that sometimes durabolin has no effect at all.

In April, 1953, a woman aged 42 felt a strand with three small lumps in the right axilla. When in the course of that year the nodules grew larger she went to see her doctor, and after a biopsy specimen had been taken she had an operation. She had never felt anything in her breast. Post-operative radiotherapy was given and she remained in good condition till July, 1955, when she began to complain of pain in her back and lack of appetite. An *x*-ray picture showed a shadow in the right lung. The blood sugar was 50–94 mg./100 ml. In the evenings the temperature was subfebrile. After a few weeks' rest in bed her condition had slightly improved, but the subfebrile temperature remained.

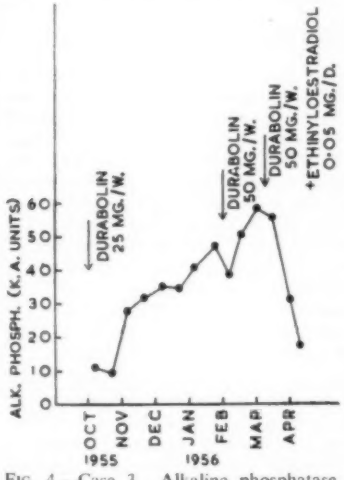

FIG. 4.—Case 3. Alkaline phosphatase during treatment with durabolin and ethinyloestradiol.

Durabolin therapy was now instituted—first 25 mg. every fortnight, later every week. As a result the patient began to look better, but the pain in the back did not diminish. In January, 1956, this pain had increased. In an *x*-ray film the shadow in the right lung had gone, but there were now clear metastases in the ninth and tenth ribs. The temperature had gone up to 38.5° C. No metastases were observed in the vertebral column. An increase of the durabolin dosage to 50 mg. weekly produced no results.

As regards the alkaline phosphatase level, this had shown a continuous increase ever since October, 1955, till it reached nearly 60 K.A. units in March, 1956. In addition to the durabolin, 0.05 mg. of ethinyloestradiol was now given daily. It is remarkable that the alkaline phosphatase then fell to 17 K.A. units (Fig. 4). However, the pain in the back remained and the patient's condition deteriorated rapidly. Skin metastases began to develop also, and she died in May, 1956.

Comment

The three cases described here, and also the other 10 with marked metastases, show that in such cases we cannot expect a cure with durabolin, but, with the exception of a single case, mentioned above, durabolin temporarily had an excellent effect. In one case calcification was observed in some of the metastases, as is sometimes seen after administration of testosterone propionate. Virilization symptoms were practically absent, and in no case did they bring inconvenience. Whether it is possible by means of durabolin to suppress metastases right at the beginning is, as already stated, obviously very hard to prove.

All eight patients who had no marked metastases but who gave cause for anxiety—for example, because the carcinoma was present during pregnancy or because they complained of vague and varying "rheumatic" pains—showed an excellent response and at the time of writing were free from cancer symptoms. All things considered, durabolin may justifiably be regarded as a valuable aid in the struggle against mammary carcinoma and as a preparation with clear advantages over testosterone propionate, the palliative value of which is established.

Summary

After a discussion on the effect of certain hormones used so far in the treatment of mammary carcinoma, including the new preparation durabolin (norandrostenolone phenylpropionate), some clinical results obtained with this preparation are reported.

It has been found that durabolin is usually a powerful and long-acting palliative which, owing to its very slight virilizing action, is a real asset in this treatment.

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ANTIBIOTICS IN ACUTE TONSILLITIS AND ACUTE OTITIS MEDIA

BY

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Antibiotics are absolutely necessary in the treatment of serious bacterial infections. It is questionable, however, whether these expensive and potentially dangerous drugs are really necessary to treat all the much more frequent infections of the respiratory tract that abound in general practice. When and how should antibiotics be used for these common and relatively minor infections? Opinions differ greatly on the needs and indications, but apart from "opinions" there have been no planned studies into the matter.

This paper is an attempt to assess in a general practice the proportions of patients suffering from two readily definable and very common respiratory infections—namely, acute tonsillitis and acute otitis media—who required antibiotics in order to achieve satisfactory results, and at the same time the proportions who recovered equally well on non-specific treatment.

Methods

In carrying out this investigation the patients' interests were always of the first importance and no risk was taken or sacrifice made for the sake of the experiment. In any case of doubt the specific antibiotics were used, but where possible the aims were to withhold the antibiotics for 24 to 48 hours unless there were certain definite indications.

Acute otitis media was defined as an acute condition with earache and a red drum or with a sudden onset of discharge from the ear, either following earache or arising *de novo* with no previous history of chronic ear disease. Other features, such as deafness, perforation of the drum, and the previous history, were recorded, but were not essential for the diagnosis. Cases of chronic otitis media, with a previous history of ear troubles and in which the drum was known to be abnormal before the attack in question, were excluded from this study as there could never be any prospect of the drum returning to normal, which was the aim with every case treated here. During the three years 41 such cases were seen, all in adults over 20, and they were all excluded.

Acute tonsillitis, or, more accurately, an acute infection of the fauces, because in some the tonsils had already been removed, was taken to mean a condition with the sudden onset of a sore throat (some young children, however, often do not complain of a sore throat and the diagnosis depends on other clinical signs) accompanied by redness and swelling of the fauces, together with a definite exudate. Although almost invariably there was some general constitutional disturbance the special level of fever was not a diagnostic criterion. Cases where the throat condition was merely part of a more generalized infection of the upper respiratory tract, as a severe common cold or influenza, were excluded.

Records were kept of all cases coming within these definitions during the years 1955, 1956, and 1957. The name, age, and sex of the patients were noted, as were the clinical details, the results of bacteriological investigations, the treatment given and the reasons for the choice of treatment, the course of the acute stage, and the state of the patient at a follow-up three months or more from the onset.

The actual procedure was to make an immediate clinical assessment of each patient when first seen, to decide whether antibiotics were then necessary. Factors considered were the severity of the infection both locally, as the degree of inflammatory swelling and the amount of pain and discomfort, and generally, as the degree of toxicity and fever; the previous history, especially of past attacks; and any individual peculiarities such as a poor state of general health, whether the patient was a nursing mother or had other important duties, whether the standards of home care were poor, and so on. Unless there were definite indications for the immediate use of antibiotics these were withheld for the first 24 to 48 hours to observe the course of the illness.

If antibiotics were given the drug used was intramuscular penicillin—either a combination of crystalline and procaine penicillins (800,000 units as "abbocillin") or this mixture plus benethamine penicillin (1,250,000 units as "triplopen"). No set "courses" were used, each case being treated individually with from one to four daily injections. In a few instances broad-spectrum antibiotics were necessary when there was no response to penicillin.

If antibiotics were withheld the patients were seen daily, or on alternate days, and symptomatic measures such as aspirin and gargles were prescribed.

A close watch was kept on all patients until the throat or the ears returned to normal. To make certain that no late complications were missed an attempt was made to see each patient at some time three months or more from the onset of the attack. At this follow-up questions were asked about the general health and whether any recurrences had occurred. The state of hearing was tested by a whispered voice at three feet, and the drums were inspected in all cases of acute otitis media. The fauces of all those who had had acute tonsillitis were examined. Few difficulties presented in following up these patients, because, except for removals, it is always very easy to establish and maintain contact with patients in the static conditions of general practice, where as a rule each patient is seen on an average three to four times a year.

During the three years 1955–7 there occurred in this practice 482 attacks of acute tonsillitis affecting 405 individuals and 552 attacks of acute otitis media in 422 individuals. The individual rate per 1,000 at risk for the practice each year for acute tonsillitis was 27 per 1,000 and for acute otitis media 28 per 1,000.

Acute Tonsillitis

The 405 patients consisted of 182 males and 223 females.

Table I shows the age distribution of all the attacks, and, bearing in mind the routine procedure that was followed, the proportions of attacks that required antibiotics and those in whom they were not used.

TABLE I.—*Acute Tonsillitis—Age Distribution and Proportions of Attacks that Required Antibiotics*

Age:	0–	5–	10–	20–	30–	40–	50+	Totals
Non-streptococcal:								
No antibiotics	19	46	29	31	16	8	10	159 (81%)
Antibiotics used ..	2	1	9	9	6	4	6	37 (19%)
	21	47	38	40	22	12	16	196
Haemolytic streptococcal:								
No antibiotics	12	67	30	30	48	12	2	201 (70%)
Antibiotics used ..	4	12	8	17	31	10	3	85 (30%)
	16	79	38	47	79	22	5	286
	37	126	76	87	101	34	21	482

Antibiotics were not used in 360 (75%) and used in 122 (25%).

It will be seen in Table I that the attacks are subdivided into those in which haemolytic streptococci were found and those in which they were not found. This is a little artificial, because it is not possible to make an accurate clinical diagnosis of the causal organism and one has to await the results of the bacteriological examinations. Treatment has therefore to be planned before the exact aetiology is known. It is interesting, however, to note that, even so, the rate with which antibiotics were used was appreciably higher (30%) in the streptococcal group than in the non-streptococcal group (19%). Among other causes were glandular fever in 8, Vincent's angina in 12, and monilia in 10. The rates for antibiotics were much higher in adults than in children because of the greater severity of the infection.

The reasons for using antibiotics in the 122 cases were: severity of the illness, 88; no satisfactory progress within 48 hours, 17; previous history, 11; and other reasons, 6.

The course of the attacks in those treated with antibiotics and those treated with non-specific methods could not be compared, because the former were highly selected and more severely affected. Nevertheless, the periods (to the nearest day) from onset for the fauces to return to normal were six days in the antibiotic group and five days in the others.

The response to penicillin was good and immediate in all but 30 (8 with glandular fever, 13 with no specific organisms in throat swabs, and 9 in which haemolytic streptococci were isolated). In the untreated group the natural improvement began to occur about 72 hours from the onset, and in only 17 of this group was penicillin eventually used because of unsatisfactory progress.

Complications.—There were no real complications in this series, either in the cases treated with antibiotics or in those treated with non-specific measures. This tends to confirm the fact that acute tonsillitis is now a relatively benign condition. There were two cases of *quinsy*, which were treated with antibiotics from the outset and cannot be termed complications. No case of *rheumatic fever* has been seen in this practice for the past 10 years, and there were none in this series. One little girl developed a classical *acute nephritis* two weeks after an acute streptococcal tonsillitis which had been treated with penicillin within 48 hours of onset. She eventually made a complete recovery.

Recurrences.—There were 65 patients who had more than one attack of acute tonsillitis during the period under review. Their age distribution is interesting, and is shown in Table II. The numbers of these recurrences are shown in Table III. The majority of the recurrences were in

TABLE II.—*Ages of 65 Patients with Recurrences of Acute Tonsillitis*

Age:	0–	10–	20–	30+	Total
Number	11	10	28	16	65

TABLE III.—*Recurrent Attacks of Acute Tonsillitis in* 1955–8

No. of Attacks	No. of Patients	Total No. of Attacks
1	340	340
2	54	108
3	10	30
4	1	4
	405	482

adults and not very severe. The child with four attacks had them all within nine months and has for the past two years been quite free of further troubles.

Follow-up three or more months after the acute attack was possible in 389 patients, and, apart from those who suffered recurrences and the little girl recovering from nephritis, all were well. Two of the patients with recurrent attacks, all adults, were advised to have their tonsils out, and did so.

Acute Otitis Media

During the three-year period there were 552 attacks of acute otitis media affecting 422 individuals (230 males and 192 females). In 85 there was more than one attack. These excluded 41 episodes of acute exacerbations in adult patients who were thought to be suffering from chronic otitis media.

Clinically acute otitis media in general practice is essentially a condition of young children (80% of cases were in children under 10). Without a doubt the condition has changed from the days when Abercrombie (1957), some 25 years ago, found that in 10% a mastoidectomy was necessary and in no less than half a myringotomy was performed. It is now generally agreed that it is a mild condition (M.R.C., 1957). Whether this has been the result of the introduction of antibiotics or coincidental with this is uncertain. It is also uncertain whether we should still regard the condition as one requiring a full course of antibiotics.

There are a number of different clinical varieties of acute otitis media, ranging from earache and a red drum in a child who does not appear to be very much disturbed to a discharging ear in a feverish and toxic patient. It is of importance to differentiate between these groups because their definition will help in deciding the needs for specific therapy.

Table IV shows the distribution of the attacks of acute otitis media in ages and also in two clinical groups—that with presenting features of earache and red drum (64% of all the attacks) and the type where there was in addition discharge from the ear (36% of the total). The proportion of the attacks in the two groups that required antibiotics is also shown. There were no appreciable differences in the proportions requiring antibiotics at the various ages.

TABLE IV.—*Acute Otitis Media—Age Distribution and Proportion of Attacks that Required Antibiotics*

Age:	0–	5–	10–	20–	30–	40–	50+	Totals
Painful ear with red drum:								
No antibiotics ..	92	136	42	6	15	9	1	301 (85%)
Antibiotics used	26	17	5	—	3	2	1	54 (15%)
	118	153	47	6	18	11	2	355
Discharging ear:								
No antibiotics ..	48	61	8	4	5	3	—	129 (66%)
Antibiotics used	30	29	3	4	—	1	1	68 (34%)
	78	90	11	8	5	4	1	197
	196	243	58	14	23	15	3	552

Antibiotics were used in 122 (22%) and not used in 430 (78%).

As in acute throat infections, the routine followed depended on the initial assessment, when the decision was made whether to use antibiotics at once or to wait and observe progress over the next 24 to 48 hours. In arriving at a decision account was taken of the severity of the illness, the degree of pain, and the extent of the general systemic upset; the previous history was of importance, antibiotics being more readily employed when there had been a number of previous attacks; then there were always special circumstances, such as social factors and other family and personal situations.

If antibiotics were not used the patient was examined daily or on alternate days. If no improvement was obviously occurring within 48 hours then antibiotics were given.

Reasons for Using Antibiotics.—In the 122 attacks these were: severity of illness, 17; no satisfactory progress within 48 hours, 63; previous history, 32; and other reasons, 10. Antibiotics were used in 22% of all the attacks, but the proportions were very different in the group without discharge and in that with discharge. Those with a painful ear and a red drum required antibiotics in only 15% of the attacks, whereas in those with discharge the rate was 34%. The reasons for the differences were chiefly that there was no definite improvement in the amount of discharge in many of the patients within the specified 48 hours.

Course.—Patients were kept under observation until the drum and the hearing returned to normal. This period of observation varied from case to case, but the average time was nine days in those without discharge and 16 days in those with discharge. In five patients the progress was very slow and oxytetracycline was used in an attempt to obtain a quicker resolution. Any comparison of the periods in the patients treated with and without antibiotics would be quite fallacious, as the cases were very highly selected, but for what they are worth the average time for recovery in those treated without antibiotics was nine days and in those treated with antibiotics it was 15 days.

Complications.—Here again there were no serious complications in any of the patients observed. No cases were referred to a consultant for advice, let alone for any active surgical treatment. Myringotomy was not necessary. In five patients the condition took more than four weeks to return to normal, but these anxieties were the only ones encountered.

Recurrences.—The natural history of acute otitis media is that it is a recurring condition of early childhood with a definite tendency towards spontaneous remission around the age of 7–8 (M.R.C., 1957). This was also found in the present survey, for the recurrent attacks in 85 patients whose ages are shown in Table V were almost all in children

TABLE V.—*Ages of Patients with Recurrence of Acute Otitis Media*

Age:	0–	10–	20–	30+	Total
Number ..	79	4	1	1	85

TABLE VI.—*Recurrent Attacks of Acute Otitis Media in* 1955–8

No. of Attacks	No. of Patients	Total No. of Attacks
1	337	337
2	58	116
3	14	42
4	10	40
5	1	5
6	2	12
	422	552

under 10 years of age. The numbers of recurrences are shown in Table VI. Almost all these recurrences were in children between 4 and 8 years of age, and they tended to occur fairly rapidly over a period of 18 months to 2 years. Even in the two children with six attacks, these all occurred over a couple of winters, with complete recovery of drum and hearing to normal.

Follow-up.—It would be ridiculous to consider the advisability of a lower rate of use of antibiotics if on follow-up an appreciable number of deaf or discharging ears or abnormal-looking drums were found. A careful follow-up was therefore necessary, and every attempt was made to see the patients three months or more from the original attack. All but seven of the 422 patients were seen—many more than once, some for a variety of other unrelated reasons. The mothers and the patients were questioned about any disabilities, and the ears were examined and the hearing was tested by ability to hear the whispered voice at three feet. Hearing appeared to be quite normal in all except three children, aged 5, 6, and 8, who were still suffering from recurring upper respiratory infections, and in whom there was a slight, but almost certainly temporary, impairment of hearing. No patient had a chronic discharging ear, and the drums appeared normal in all but the three referred to above, in whom there was thickening of the drum. The follow-up included all the 85 patients who suffered more than one attack of acute otitis media, and in these, too, the results were as satisfactory as in those who had had only one attack, with the exception of the three referred to.

Discussion

Although it is 15 years since penicillin first became widely available there are still no uniform views concerning the real indications and the best methods of use in the infections met with in general practice. The great importance of this field as one worthy of study is the fact that by far the largest proportions of antibiotics are prescribed by general practitioners. In 1956, out of a total of £11m. spent on antibiotics in Great Britain, those prescribed by general practitioners accounted for not less than £9m. (Ministry of Health, 1957, personal communication).

The prescribing habits of family doctors vary greatly. In my own practice antibiotics are used in only a quarter of all cases of acute tonsillitis and acute otitis media, with excellent results. Wheatley (1957), on the other hand, pleads that in acute tonsillitis "no patient should be denied the prophylactic and therapeutic benefits of antibiotics." In a survey by a faculty of the College of General Practitioners of some 261 cases of acute tonsillitis treated by a group of family doctors, antibiotics or sulphonamides were used in no less than 72% (W. H. J. Lord, 1957, personal communication). An M.R.C. report on acute otitis media in general practice showed an amazing range of different therapeutic habits amongst the 13 practices taking part. In seven antibiotics were used in over 90% of cases of acute otitis media; in three the rates were between 89% and 65%; and in three antibiotics were used in less than one-third. The results of all these groups were apparently equally satisfactory.

These rates are all higher than those found necessary in this particular study, and, taking into consideration the very satisfactory results achieved here with a low rate of usage, the question is raised, In how many cases of acute otitis media and acute tonsillitis are antibiotics being used unnecessarily?

In considering this question it is also necessary to remember that these drugs are not absolutely safe and they are expensive, that even in pre-antibiotic days the majority of these infections settled without any permanent effects, and that there has certainly been a diminution in virulence of the streptococci which account for so many of these conditions.

Summary and Conclusions

An attempt has been made to investigate the needs for antibiotics in the management of acute tonsillitis and acute otitis media on the supposition that not all of these infections require such specific measures.

During the three years 1955–7 all cases of acute tonsillitis and acute otitis media occurring in a South London general practice were recorded, observed, and followed up. There were 482 attacks of acute tonsillitis affecting 405 individuals, and 552 attacks of acute otitis media in 422 individuals.

The procedure followed was to withhold penicillin (the antibiotic used) unless there were definite indications, and to follow the course carefully, always prepared to use the antibiotic where necessary.

With this routine antibiotics were required in 25% of all attacks of acute tonsillitis—19% in the non-streptococcal group and 30% in those in whom haemolytic streptococci were found in throat swabs. In acute otitis media antibiotics were needed in 22% of all the attacks—in 15% with a painful eardrum and in 34% where there was discharge from the ear.

The results in these cases were eminently satisfactory. No real complications occurred in either group, and on follow-up three months or more later only three children were found to be slightly deaf, with abnormal drums. There were no chronic discharging ears, and in other patients drums were not regarded as abnormal. Recurrent attacks were common. 65 patients had more than one attack of tonsillitis and 85 had more than one attack of acute otitis media.

This relatively small and highly personal study by one general practitioner on his own practice in one part of the country presents a pattern that might not apply wholly to the rest of the country. It does suggest, however, that it would be worth while looking further into our habits of using antibiotics.

Very large proportions of cases of acute tonsillitis and acute otitis media would seem to settle naturally and safely without the need for specific drugs, and many of us might be using these drugs unnecessarily. Admittedly it requires a considerable amount of clinical courage at first to alter our set habits and to withhold drugs that we have been in the custom of using routinely with excellent results, but, once the initial decision is made to wait and see for a day or two before using them, it is astounding how many cases of acute tonsillitis and acute otitis media will recover on their own.

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The rehabilitation of the newly blind is one of the subjects covered in the report of the executive council of the Royal National Institute for the Blind for the year ending March 31, 1958. The Institute has two residential rehabilitation centres (at Torquay and Bridgnorth) where the newly blind are taught how to become useful and independent citizens again. Training and employment is another subject discussed, and it is stated that the trained blind worker is found to-day in ever-increasing numbers holding his own in industry and commerce in competition with the sighted. There is a commercial training college in London where blind persons selected for ultimate employment as shorthand-typists, recorder-typists, and telephone-switchboard operators are trained. Those interested in light engineering are able to receive their basic training at the Government training centre at Letchworth; they then receive further training in the factory by the Institute's training officers. The Institute found employment for 293 trained blind persons during the year, bringing the total number of placements since the service was inaugurated in 1942 to 3,869. The report is obtainable from the Royal National Institute for the Blind, 224, Great Portland Street, London, W.1.

ARTIFICIAL RESPIRATION

COMPARISON BETWEEN MANUAL AND INTERMITTENT POSITIVE-PRESSURE METHODS

BY

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The essential feature in the treatment of acute respiratory failure from any cause is adequate ventilation. Although the Schafer and, more particularly, the Holger Nielsen methods of manual artificial respiration are acceptable under most circumstances, there may be occasions when they are not practicable; for example, when there is injury to the chest or upper limbs, in confined surroundings, or when there is partial respiratory obstruction, such as that due to bronchospasm. It might therefore be desirable to have some other means of resuscitation that does not suffer from these limitations. The aim of this investigation was to examine the merits of intermittent positive-pressure ventilation as achieved by a modification of the classical mouth-to-mouth respiration, or by a simple hand-operated bellows resuscitator, and to compare it with the conventional Schafer and Holger Nielsen methods under similar conditions.

Methods

For obvious reasons it was not possible to investigate the efficiency of these forms of artificial respiration under field conditions, but a comparison could be made by ventilating anaesthetized, curarized subjects undergoing elective surgery. Fit patients between the ages of 20 and 40 years were selected. All were premedicated with "omnopon," 20 mg., scopolamine, 0.4 mg., and an amethocaine lollipop. They were induced with thiopentone, 0.75–1 g., and tubocurarine, 20–30 mg. A No. 10 Magill cuffed, endotracheal tube was inserted under direct vision to ensure a perfect airway. Anaesthesia and respiratory paralysis were maintained by the further administration of small doses of thiopentone and tubocurarine when necessary.

The efficacy of artificial respiration could not always be assessed from identical parameters. The oxyhaemoglobin content of the blood, using an ear oximeter, was determined in all the methods. Tidal volumes were measured by means of a spirometer in the manual methods. With mouth-to-mouth ventilation expired air was collected into previously vacuumized Barcroft tubes from a point at the mouth end of the endotracheal tube at the end of expiration and subsequently analysed.

Manual Methods

Ten subjects were placed face down on a sorbo-rubber mattress of 1¼ in. (4 cm.) thickness laid on the floor. The patient's endotracheal tube was connected directly to a spirometer filled with air. Flow was so arranged that only normal air reached the patients, who were respired at 16 times a minute for five minutes by the Schafer method, followed by five minutes with the Holger Nielsen method. Care was taken to adhere in detail to the procedures laid down by the authors of the methods (Schafer, 1904; Nielsen, 1932).

Intermittent Positive-Pressure Methods

(1) The *mouth-to-mouth apparatus* consisted primarily of a standard light-type Service respirator worn by a donor. The respirator was slightly modified in that inside the facepiece a mouth-piece was fitted over the outlet valve and the nose of the valve was connected to a piece of corrugated tubing. The other end of this tubing was attached to an oronasal mask which could be held over the recipient's face. Valving was achieved manually by the donor closing a hole in the short connecting tube between the flexible hose and the oronasal mask during his exhalation (Fig. 1). Fourteen

FIG. 1.—Photograph of mouth-to-mouth apparatus.

subjects were ventilated for 30 minutes by the same donor. On six occasions the apparatus was used as already described, and on the other eight occasions a carbon dioxide absorption canister was added, being placed between the outlet valve of the respirator and the corrugated tubing. All subjects were respired at 16 times a minute with moderate hyperventilation on the part of the donor. After the first few minutes this pattern of breathing could be maintained without any conscious effort. Gas samples of donor and recipient expired air were collected at five-minute intervals, the first being taken as soon as the endotracheal tube was in position.

(2) The *resuscitator* consisted of a bellows, maximum capacity 3 litres, and a face-mask, connected together by a dual purpose valve which permitted air to enter the face-mask and lungs during compression of the bellows, and allowed the subject's expired air to escape into the atmosphere during expansion, when air re-entered the bellows through a non-return valve under the back-plate. A relief valve, set to lift at 30 cm. of water, was also fixed under the back-plate. The mask and the bellows were so designed that the chin fitted into the mask, and when the bellows was operated the jaw was automatically held up, thus ensuring a clear airway (Fig. 2). Eight subjects were ventilated for five minutes, the mask being fitted over the face and not

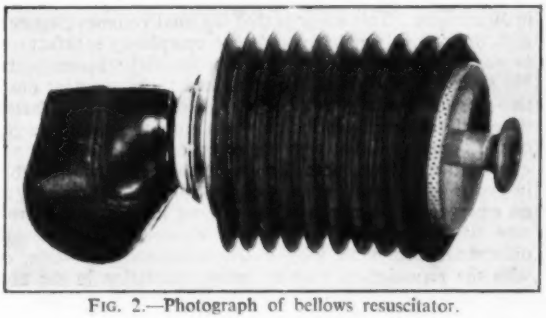

FIG. 2.—Photograph of bellows resuscitator.

connected directly to the endotracheal tube. The bellows was compressed at a rate of 16 times a minute and each stroke delivered a tidal volume of 2 litres of air, as calculated from the known volume of the bellows. It was not possible to measure the actual volume of air expired from the subject, neither were any samples taken for carbon dioxide analysis, as there was no rebreathing.

This method of resuscitation was also used for ventilating a further series (53) of patients undergoing surgery under thiopentone and tubocurarine anaesthesia for 30 minutes and upwards.

Results

Manual Methods.—As measured by oximetry, the blood saturation in all these subjects remained above 90%. There was, however, a slight fall during the experiment in practically every case. The mean tidal volumes obtained by the Schafer and Holger Nielsen methods were 262 ml. and 575 ml. respectively (see Table).

Tidal Volumes

Subject	Sex	Tidal Volumes (ml.)	
		Schafer	Holger Nielsen
1	M	230	580
2	F	300	900
3	M	200	450
4	F	350	500
5	F	240	450
6	F	170	320
7	F	350	750
8	F	360	800
9	F	170	590
10	F	250	410

Intermittent Positive-pressure Methods.—(1) With *mouth-to-mouth* respiration oximetric studies were undertaken on the first few patients in each group—that is, with and without the carbon dioxide absorber in the donor expired air circuit. As the oxygen saturation never dropped below 96%, oximetry was discontinued for the remainder of the experiments. The mean results of the carbon dioxide and oxygen concentrations of the expired air of the donor are shown in Fig. 3, and those of the recipient, with and without canister, in Fig. 4. With the canister the expired oxygen concentration of any patient did not fall below 14.15%, and the carbon dioxide did not rise above 5.7%. Without the canister the lowest expired oxygen concentration was 11.4%, and the highest carbon dioxide concentration 6.4%. (2) With the *bellows resuscitator* oximetry showed that no change occurred in the blood oxygen saturation of the eight subjects during the period of ventilation, and clinically there was no deterioration in their condition.

In the larger series ventilated by the bellows during surgery it was in no case possible to distinguish their clinical condition from that obtained with an ordinary, controlled respiration, anaesthetic technique.

Discussion

In this investigation all four forms of artificial respiration were found to be adequate for maintaining oxygenation of the anaesthetized, curarized subject under ideal conditions, but, whereas there was a slight fall-off in oxygen saturation with manual methods in five minutes, no such fall occurred with either form of positive-pressure resuscitation in 30 minutes. This suggests that the tidal volumes obtained with the manual methods were not completely satisfactory, as was in fact confirmed by the experimental measurements. No such deficiency could be attributed to intermittent positive-pressure artificial respiration, where the limiting factor in mouth-to-mouth ventilation was simply the vital capacity of the donor, and that with the resuscitator the 3-litre capacity of the bellows, both these volumes being considerably in excess of the requirements of any subject. Therefore, in an emergency, when conditions are not ideal, positive-pressure would be more effective. Moreover, the pressure differential obtainable with mouth-to-mouth respiration, or with the resuscitator, enables better ventilation in the presence of respiratory obstruction, such as bronchospasm.

It has been argued, with little if any evidence, that positive-pressure ventilation inflates the stomach to the detriment of the lungs. There is evidence that this is not so at pressures up to 20 cm. of water (Mushin and Morton, 1958). Even if it were, a state of equilibrium would ultimately be reached in which both the lungs and the stomach would be ventilated. Positive-pressure respiration has also been criticized on the grounds of impairment of the venous return to the heart, but if the respiratory pressure is dropped to zero in between each breath venous return is not impeded, as judged by the absence of any change in mean venous pressure. The essential feature of any form of resuscitation is that the blood reaching the left side of the heart should be well oxygenated, even if the amount is a little reduced.

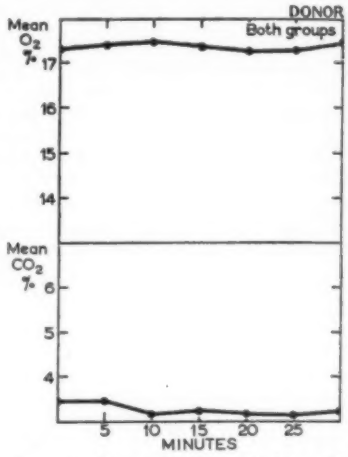

FIG. 3.—Mean carbon dioxide and oxygen concentration of expired air of donor.

In the two methods of intermittent positive - pressure respiration used in this investigation there was found to be little difference if the carbon-dioxide canister was included in the donor line of the mouth - to - mouth apparatus. When normal expired air was used the patients showed the typical clinical picture of respiratory acidosis under anaesthesia—namely, a flushed skin and a raised pulse rate and blood pressure — and needed an increased amount of barbiturate to maintain the same level of anaesthesia. Such a state has been shown by several authors to predispose to shock (Beecher and Murphy, 1950; Lucas and Milne, 1955). With a canister this form of resuscitation is satisfactory, but, in practice, any suitable canister would soon become exhausted and so replacements would have to be an integral part of the equipment. Apart from aesthetic considerations, an overall disadvantage of mouth-to-mouth ventilation is that there is a tendency on the part of the donor to overventilate, which must ultimately produce fatigue. The bellows resuscitator, on the other hand, has been shown to be entirely satisfactory: there are no components which have to be exchanged, fresh atmospheric air is used for each breath, there is minimal fatigue, and the complete apparatus is extremely simple.

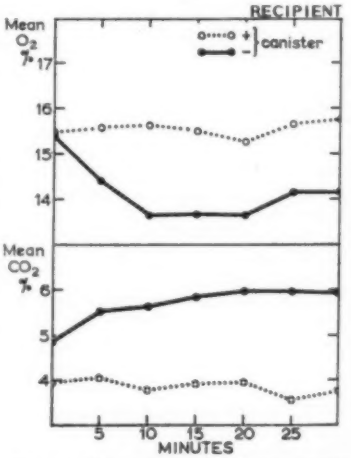

FIG. 4.—Mean carbon dioxide and oxygen concentration of expired air of recipient (with and without canister).

Summary

The relative merits of manual and intermittent positive-pressure artificial respiration have been investi-

gated in the unconscious, curarized subject. The Schafer and Holger Nielsen methods have been compared with mouth-to-mouth ventilation and a simple bellows resuscitator.

Manual methods have the advantage of requiring no apparatus, but they do require space. They are not so efficient for the oxygenation of the subject and may be relatively ineffective in the presence of bronchoconstriction.

Intermittent positive-pressure methods require apparatus, but are superior in terms of ventilation and oxygenation. The bellows resuscitator, a simple, compact apparatus, was still more efficient than the mouth-to-mouth apparatus.

The bellows resuscitator used in this investigation was designed and supplied by the Chemical Defence Experimental Establishment, Porton, Salisbury.

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CLINICAL EVALUATION OF "MIRADON"

BY

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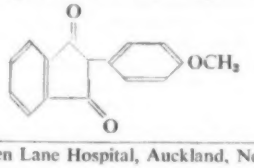
The value of anticoagulants in the treatment of certain thrombo-embolic conditions is now well established. Since the introduction of dicoumarol about 17 years ago (Butt *et al.*, 1941 ; Wright and Prandoni, 1942 ; Overman *et al.*, 1942), a number of hydroxycoumarin and indanedione derivatives, causing depression of the prothrombin activity of blood, have become available for use as anticoagulants. In addition to dicoumarol, these include ethyl biscoumacetate ("tromexan") (Tulloch and Gilchrist, 1951 ; Burke and Wright, 1951), phenindione ("dindevan") (Jaques *et al.*, 1950), phenylpropylhydroxycoumarin ("marcoumar") (Bourgain *et al.*, 1954), cyclocoumarol ("cumopyran") (Hanson *et al.*, 1951), and, more recently, warfarin (Clatanoff *et al.*, 1954) and nicoumalone ("sintrom") (Weiner *et al.*, 1956). They all suffer the disadvantage of being potentially dangerous and require frequent estimations of the prothrombin time for their control. As yet, however, they remain the best available drugs for treatment where prolongation of the prothrombin time is desired.

The purpose of this paper is to report the clinical trial of a new anticoagulant, 2-*p*-anisyl indanedione–1,3($C_{16}H_{12}O_3$), called "miradon" (anisindione). It appears to be more rapidly effective than and just as readily controlled as any anticoagulant in current use.

Material and Methods

Miradon has previously been tested in animals (P. L. Perlman and P. C. Giordano, unpublished work) without evidence of toxicity. It has the following chemical structure.



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Like phenindione, to which it is chemically related, miradon exercises its therapeutic action by depression of the prothrombin activity of the blood. In the presence of alkaline urine an orange colour is often detected, the result of katabolites of miradon.

Miradon was supplied in 50-mg. tablets for oral use, and the clinical trial was divided into three parts.

Part I.—A loading dose of 300 mg. was given to 12 healthy subjects, and the onset, rate, degree, and duration of prothrombin activity depression were recorded. None of these patients required anticoagulant therapy and all were free from known renal or hepatic disease. Estimations of the prothrombin time were performed according to the Quick one-stage method (Quick, 1942), using a phenol-saline preparation from human brain as a source of thromboplastin. Each batch of thromboplastin was diluted to obtain prothrombin % activation curves, and the results presented here are given as prothrombin % activity. The normal control using this method varied from 11 to 14 seconds. Prothrombin activity of 10 to 20% was regarded as a satisfactory therapeutic range ; this corresponds approximately to two to three times the normal plasma prothrombin time. Prothrombin activation curves were obtained for each patient.

Part II.—This constituted a therapeutic trial in 25 patients in whom anticoagulant therapy was thought to be necessary. These patients comprised 25 consecutive admissions who would otherwise have received therapy with another anticoagulant. Of these patients, 20 were suffering from a recent myocardial infarct, two from acute coronary insufficiency of increasing severity, two from deep venous thromboses of the legs (one of these had also suffered a pulmonary infarct), and one patient was given anticoagulant therapy while he received treatment to convert auricular fibrillation to normal rhythm. The aim in treatment was to maintain the prothrombin activity between 10 and 20%, and the dose for patients was ordered each day by the one observer. Estimations of the prothrombin time were performed before treatment began, 24 hours later, and thereafter daily between 9 and 10 a.m. for the first two weeks and for two out of every three days thereafter until treatment had been completed. During the course of this trial, random 24-hour periods were studied more closely to observe variations in prothrombin activity. The initial dose was 300 mg., except in three patients suffering from myocardial infarction in whom cardiac failure was present. (In these patients the initial dose given was 250 mg.) After 24 hours a further dose of 100 mg. was given, and thereafter the single daily dose depended upon the prothrombin times.

Part III.—The effect of oral vitamin K_1 on the prothrombin time was observed in a number of patients in whom "therapeutic levels" had been maintained for at least three days. The effect of vitamin K_1 was assessed further by the simultaneous oral administration of 20 mg. together with 300 mg. of miradon.

Results

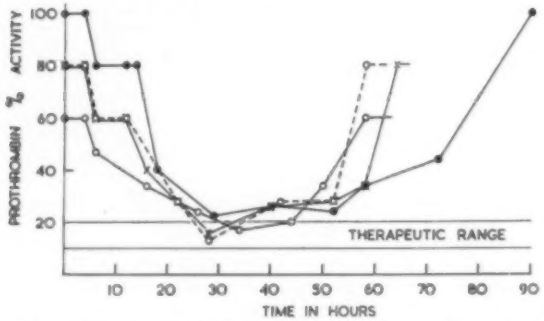
Part I

In 11 of the 12 subjects given 300 mg. of miradon orally there was an effect upon the prothrombin time within six

TABLE I.—*Effect of a Loading Dose of 300 mg. of Miradon*

Subject	Duration of Effect (Hours)	Prothrombin % Activity at Start	Prothrombin Activity Less than 25% (Hours)	Maximum Effect	
				Prothrombin %	Time (Hours)
1	6–64	40	24–52	12	34
2	8–106	50	26–58	17	50
3	4–58	100	—	30	26
4	6–58	60	26–38	17	34
5	6–96	40	20–52	14	28
6	6–72	47	26–38	17	34
7	6–58	40	20–40	13	34
8	6–96	100	26–58	22	28
9	6–64	80	22–40	13	28
10	6–60	80	22–46	16	28
11	6–58	80	—	30	30
12	6–52	100	—	28	26

hours (Table I). In one subject no effect was evident before eight hours, while in another prolongation of the prothrombin time occurred within four hours. After a sharp fall in prothrombin activity to the region of 50 to 70% of the original level there was a slower decrease over the ensuing 4 to 10 hours, followed again by a steeper fall to the maximum effect, which was present between 20 and 50 hours (average 34 hours). The average duration of effect was from 6 to 70 hours, with an overall range of 4 to 106 hours. Seven of the 12 subjects were within the average range. Typical prothrombin activation curves are illustrated in the Chart. The trial dose was sufficient to produce the desired therapeutic level of 10 to 20% prothrombin activity in 8 of the 12 subjects, while in the other 4 the lowest level produced was between 21 and 30%.



Effect of 300 mg. of miradon upon prothrombin activity in four subjects.

By way of comparison, 12 similar subjects were given 200 mg. of phenindione. The average duration of effect was from 10 to 60 hours, with an overall range of 8 to 100 hours. Eight of the 12 subjects were within the average range, while the average maximum effect occurred at 30 hours. In these subjects the lowest level of prothrombin activity produced by this loading dose varied from 16 to 49%. This may be compared with the range of 12 to 30% observed above with miradon.

Part II

A satisfactory therapeutic effect upon the prothrombin activity was obtained in all patients (Table II). The prothrombin activity was within the therapeutic range (10–20%) within 24 hours of the initial dose in 16 of the 25 patients. When these results are combined with those obtained in Part I, 56% of the 37 subjects had prothrombin activity within the therapeutic range at 24 hours, and a further 30% had a prothrombin activity between 21 and 24% (Table III). After the first 24 hours, 86% of the 472 estimations of the prothrombin time performed were within the therapeutic range, 7% were narrowly outside this range (21–24%), and only 2% occurred in the 25 to 30% group. There were no estimations showing less satisfactory control than this, and, of the 5% recorded as having a prothrombin activity of less than 10%, the most prolonged prothrombin time was one of 62 seconds at a time when the control was 14 seconds.

The uniformity of prothrombin activity as a result of single daily doses of miradon was demonstrated by closer observation of random 24-hour periods in eight patients (Table IV). Little significant variation was evident throughout these periods.

TABLE II.—*Response in Prothrombin Activity 24 Hours After the Initial Loading Dose of 300 mg. of Miradon and the Percentage of Subsequent Prothrombin Estimations Within Therapeutic Levels*

Name	Age	Prothrombin Activity at 24 Hours	Days Treated	% Results with Prothrombin Activity 10–20%
H.R.	49	28	28	79
A.J.	80	16	25	88
J.M.	71	17	26	90
T.U.	67	21	28	78
J.H.	75	21	26	80
J.McF.	37	16	21	81 (Died)
G.C.	49	20	26	90
F.W.	51	15	26	72
E.McA.	52	26	26	90
H.K.	65	23	26	87
R.C.	65	23	27	83
J.R.	66	13	26	94
W.A.	56	20	27	95
E.McA.	55	16	5	67 (Died)
A.L.	58	16	28	81
J.S.	56	17	26	84
M.W.	42	17	26	95
I.B.	58	18	36	75
A.S.	56	16	26	94
J.McC.	56	19	26	94
A.H.	45	22	12	86
I.G.	77	22	27	100
J.G.	66	20	27	94
J.McK.	72	19	27	87
M.S.	56	24	26	87

TABLE III.—*Effect of 300 mg. of Miradon on the Prothrombin Activity at 24 Hours*

Prothrombin Activity at 24 Hours	No. of Patients	% of Total
Less than 10%	0	0
10–20%	21	56
21–24%	11	30
25–30%	5	14

TABLE IV.—*Uniformity of Prothrombin Levels Throughout Random 24-Hour Periods in Eight Patients Treated with Miradon*

Subject	0 Hours	8 Hours	12 Hours	20 Hours	24 Hours
1	13	11	10	11	11
2	11	13	11	10	11
3	17	18	19	20	19
4	14		18	15	15
5	12	12	18	14	15
6	12	11	12	10	12
7	12	13	14	12	12
8	12		15	11	13

Once therapeutic levels had been obtained, the daily maintenance dose varied from 25 to 350 mg. In two-thirds of the patients the variation between maximum and minimum doses required to maintain therapeutic levels was 100 mg. or less. The average maintenance dose was 100 mg. a day. One instance of mild resistance was noted in a patient in whom there was an initial satisfactory response to 300 mg. and subsequent doses of 100 mg. a day. It became necessary to increase the dose by stages to 350 mg. a day to maintain control. This patient was later treated with phenindione, to which he showed a more marked degree of resistance, and doses of 550 mg. daily were necessary to produce therapeutic levels. In the remaining 24 patients the maintenance dose varied from 25 to 250 mg.

The time taken for the prothrombin level to return to normal on discontinuation of therapy was observed in 10 of the 25 patients. In all instances at 24 hours the prothrombin activity was within 3% of the previous reading. At 32 hours the prothrombin time of two patients had returned to normal, and by 72 hours normal prothrombin times were recorded in all 10 patients.

Throughout these trials toxic side-effects were not observed, there were no haemorrhagic episodes, haematuria was not encountered, and in those patients in whom liver-function tests were performed prior to treatment no change was observed after therapy.

Part III

Vitamin K_1 given orally in doses of 20 mg. produced an appreciable response on the prothrombin time within four to six hours, and in six subjects normal levels were produced within 10 to 12 hours. Vitamin K_1 in 20-mg. doses given intravenously resulted in a fall to normal levels within four hours. A similar oral dose of vitamin K_1 given together with the loading dose of miradon resulted in an absence of subsequent hypoprothrombinaemia. Miradon was thus satisfactorily antagonized by vitamin K_1.

Discussion

In general, anticoagulants may be used therapeutically either in short courses of 14 to 28 days, as in deep venous thrombosis and recent myocardial infarction, or for more prolonged therapy in the prophylactic treatment of coronary thrombosis or embolic phenomena.

Ideally, anticoagulants must be free from toxic side-effects. In addition they should be readily metabolized and excreted. They should maintain the prothrombin time within therapeutic levels and without wide variations. In the event of spontaneous haemorrhage a rapid reversal of anticoagulant action with vitamin K_1 is necessary. In these days of increasing Health Service costs they should also be reasonably priced. In short-term therapy the requirements are more exacting, and, in addition to the "ideals" already mentioned, a rapid, uniform, and predictable response to a standard dose is highly desirable. Equally important is the uniformity of prothrombin time response from day to day, so that any doctor unaccustomed to the daily regulation of anticoagulant dosage may not find control difficult.

The relative merits of the various hydroxycoumarin and indanedione anticoagulants have been fully discussed by previous workers (Brodie *et al.*, 1952; Scarrone *et al.*, 1952; Coon *et al.*, 1953; Weiner *et al.*, 1956; Prior, 1957). For long-term therapy the rapid production of therapeutic levels and early uniformity of response are not essential. Once over the initial difficulties of stabilization, most anticoagulants prove satisfactory for this form of treatment. The longer-acting anticoagulants (phenylpropylhydroxycoumarin, warfarin, and cyclocoumarol) are suitable for prolonged prophylactic therapy, but the time taken to acquire therapeutic levels and the delay in returning to these levels when control is unsatisfactory make them less desirable than the shorter-acting anticoagulants ethyl biscoumacetate and phenindione for short-term therapy.

Although ethyl biscoumacetate is very rapidly absorbed the considerable variation in dose required to produce therapeutic levels tends to offset this advantage (Weiner *et al.*, 1953; Vander Veer *et al.*, 1953). Coon *et al.* (1953) thus found that a greater percentage of patients treated with phenindione were within the therapeutic range at 24 hours than with ethyl biscoumacetate, despite its slower absorption. They found also that there was less difficulty in maintaining constant levels with phenindione, and these factors, coupled with the excessive cost of ethyl biscoumacetate, have led to the more general use of phenindione. As phenindione is, in our experience, the most satisfactory anticoagulant at present in use for short-term therapy it is important to compare this drug with miradon. With phenindione, therapeutic levels are obtained within 24 to 48 hours (Sise *et al.*, 1957), although in the majority of patients these levels take 32 to 48 hours to be produced (Blaustein *et al.*, 1950). Coon *et al.* (1953) found that 18% of their patients were controlled at the end of 24 hours, 70% at 36 hours, and 95% at 48 hours. Our own experience with phenindione is in agreement with this finding.

With miradon, 56% of patients were found to have prothrombin times in the desired range of 10 to 20% prothrombin activity within 24 hours, and 30% were narrowly outside this control. The average time taken for production of maximal effect with miradon and phenindione is very similar (miradon 34 hours, phenindione 30 hours), and for the numbers considered the difference is not significant. With miradon, however, there is a narrower range of response to the initial loading dose (prothrombin activity 13–30% compared with phenindione, 16–49%). As compared with phenindione, therefore, the response to a given dose of miradon is a little more predictable. This allows a larger initial dose to be used with safety and leads to a greater number of patients in whom therapeutic levels of prothrombin time are produced within 24 hours. In addition, in the majority of patients, miradon produces some effect upon the prothrombin time within six hours, compared with 10 hours taken by phenindione. Control from day to day appears very satisfactory with miradon, and only 14% of the estimations in this trial were not within the desired range. Our own experience with phenindione is very similar, and 15% of estimations have been found to be outside this control.

Sise *et al.* (1957) found on stopping phenindione that the prothrombin time of their patients returned to normal levels in 36 to 72 hours in the majority of patients. Miradon was found to take a similar period of time, and, as with phenindione (Guttas *et al.*, 1953), there was a rapid response to vitamin K_1.

It appears, therefore, that miradon has certain advantages over phenindione in the speed and predictability of initial response and subsequent rapidity with which therapeutic levels can be obtained. It is apparently just as readily managed from day to day, and has the advantage that a single dose produces striking uniformity of response, while most workers consider that phenindione requires to be given in divided daily doses to produce satisfactory uniformity of response (Blaustein *et al.*, 1950).

Summary

A new anticoagulant, miradon, has been assessed clinically and used therapeutically in the treatment of 25 patients requiring anticoagulant therapy.

The initial response to a loading dose of 300 mg. was rapid and some effect upon prothrombin time was evident in most subjects in six hours. Over 50% of patients had prothrombin levels within the desired therapeutic limits (prothrombin activity of 10 to 20%) at 24 hours, and 86% of subsequent estimations of the prothrombin time were within similar limits. Normal prothrombin levels were recorded between 36 and 72 hours after cessation of treatment and a very even response was evident during therapy. Vitamin K_1 produced a rapid reversal of anticoagulant action.

Compared with other anticoagulants miradon appears to approach more closely to the "ideals" for a short-term anticoagulant than other preparations at present in common use. The uniformity of response to a single daily dose suggests that it would prove satisfactory also in long-term therapy.

I thank Dr. A. Rae Gilchrist for his help and advice in conducting this trial, and Dr. C. P. Stewart for the laboratory facilities which he made available. I also thank Dr. R. M. Marquis and Dr. M. F. Oliver for criticism in preparing this paper. Miradon was generously supplied by Schering Corporation, who also provided an expense grant.

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CLINICAL EXPERIENCE WITH WARFARIN SODIUM

BY

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Several reports (Shapiro, 1953; Wolff *et al.*, 1953; Pollock, 1955) are now available on the use of the anticoagulant warfarin sodium ("coumadin" sodium), and all are very favourable. Indeed, it has been stated that warfarin sodium is the "anticoagulant of choice" (Shapiro, 1956). This paper records the results of using warfarin sodium in 175 patients, most of whom had cardiovascular disease (myocardial infarction or cardiac failure) and the remainder phlebothrombosis and pulmonary embolism. Treatment was controlled by the simultaneous use of Quick's and Owren's "P and P" methods. A therapeutic level of between two and three times the normal control time (ideally two and a half times) was maintained when assessing results by Quick's method. For Owren's technique a level of between 10 and 14% was aimed at. This percentage prothrombin concentration is lower than that advised by Owren—10 to 30%—but I believe that a lower proportion than 30% is desirable, as I have seen fresh thrombo-embolic episodes develop between levels of 20 and 30%.

The same thromboplastin was used for both Quick's and Owren's methods—that is, a saline extraction of human brain stored at −20° C., where it keeps stable indefinitely. The Quick prothrombin time with pooled plasma from normal controls was 11 to 12 seconds with this thromboplastin.

Initial Dosage

Warfarin sodium is a unique coumarin compound in that it can be given intravenously as well as by mouth. The initial dose was given intravenously to 32 patients and orally to 143. No appreciable difference in rapidity of action was noted between the intravenous and the oral administration; therefore, except for exceptional circumstances—for example, persistent vomiting—the oral route was preferable. The usually recommended initial dose of 60 to 75 mg. was given to the first 42 patients treated. This dose, however, in nearly all instances led to a pronounced rise in the prothrombin time to above the upper limit (three times the normal control time) for therapeutic control. Small doses of vitamin K_1 had to be given to six patients to bring the prothrombin time down to a safe level. For the remaining 133 patients the initial dose was therefore sharply reduced to between 35 and 50 mg., and the latter dose was never exceeded. With these lower doses the results were much more satisfactory and made the whole control of the treatment much easier.

If too big an initial dose of most coumarin-type anticoagulants is given the peak effect of the drug may be delayed for several days and a sustained effect will still be present for many days thereafter, during which time no further dose of the anticoagulant must be given. This sustained effect is obtained even with the shorter-acting drugs such as warfarin sodium and phenindione, because to some extent sustained action depends on dosage; the larger the dose the longer the effect. If too big an initial dose is given, with the resultant marked sustained effect, it takes much longer to arrive at the correct daily maintenance dose necessary to maintain a steady prothrombin time. By keeping the initial dose to the minimum effective amount, the first maintenance dose can usually be given on the third day of treatment (about 36 to 48 hours after starting therapy). Also, by avoiding the pronounced sustained effect of too large an initial dose, the early maintenance doses will give a good approximate indication of the correct subsequent doses necessary to maintain a steady prothrombin level throughout the course of anticoagulant treatment.

Very satisfactory results were obtained with the following initial dosages of warfarin sodium: doses of 35–40 mg. were never exceeded for patients over the age of 75 years; doses of 42–50 mg. were given to all patients under 75 years. The smaller doses were given to the frailer and more seriously ill patients. An initial dose of more than 50 mg. is not advised.

The first prothrombin time was taken routinely on the morning of the third day after starting treatment (usually 36 hours after the initial dose), by which time the maximum effect of the initial dose was apparent in most patients.

Rapidity and Duration of Action

With initial doses of 35 to 50 mg. a therapeutic prothrombin time was reached in 36 hours in 95% of cases, whilst a noticeable effect on the prothrombin time was achieved in about 18 hours in most instances. The effect of daily maintenance doses of a size sufficient to maintain an adequate therapeutic level usually lasts for 36 hours. If large doses of warfarin are given, however, there is a pronounced sustained effect and the prothrombin times may remain high for much longer than 36 hours, and often for three to four days.

Warfarin sodium is therefore a rapidly acting drug with a moderately short-lasting action if large doses are avoided. In rapidity of action and duration of effect it is remarkably similar to phenindione and can be classed with that drug as a short-acting anticoagulant, in contrast to the long-acting drugs such as diphenadione ("dipaxin"), dicoumarol, and phenylpropylhydroxycoumarin ("marcoumar"). However, if large doses are given it has a much more pronounced sustained effect than phenindione.

Maintenance Therapy

It was possible to arrive at a very accurate assessment of the daily maintenance dose of warfarin sodium (to within 3 to 5%) in 158 patients (see Table). The average daily maintenance dose for all patients was 9 mg. In 68% the maintenance dose was between 5 and 12 mg., and in only 20% was the maintenance dose outside the range of 5 to 15 mg.

Maintenance Doses of Warfarin Sodium in 158 Patients

Dose	No. of Patients
2 to 5 mg.	20
5 to 12 mg.	107
12 to 15 mg.	19
15+ mg.	12

Overall average=9 mg.

The first maintenance dose was usually given on the third day of treatment. The following scheme provided a good average indication of the first maintenance doses to be given:

Prothrombin time over 3 times the normal (or below 7% by Owren's method)	Nil
Prothrombin time 2½ to 3 times the normal (7 to 9% by Owren's method)	3 to 5 mg.
Prothrombin time 2 to 2½ times the normal (9 to 15% by Owren's method)	4.5 to 10.5 mg.
Prothrombin time 1½ to 2 times the normal (15 to 20% by Owren's method)	10.5 to 15 mg.
Prothrombin time less than 1½ times the normal (above 20% by Owren's method)	15 to 20 mg.

Warfarin sodium acts rapidly enough for any appreciable change in dosage to be quickly reflected in the prothrombin times. The great advantage of rapidly acting drugs, such as warfarin sodium and phenindione, over the long-acting drugs for the treatment of acute thrombo-embolic episodes is that rapid and large changes in dosage can be quickly made, with the result that the correct maintenance dose can be rapidly determined. In the first few days of anticoagulant

therapy, because of the great individual variation in response to all anticoagulant drugs, it is impossible to know whether the patient will need small or large maintenance doses. Regulation of dose has therefore to be by trial and error guided by the results of the blood tests. Thus it is a great advantage to use an anticoagulant whose action is rapid enough for any material change in dosage to be reflected in the prothrombin times the following day.

After the first few doses of maintenance therapy, and once the prothrombin time is in the required therapeutic range, it is rarely necessary to alter the daily maintenance dose of warfarin sodium by more than 1.5 to 2 mg. When the prothrombin time has been steady for three or four days it should be realized that a change in the daily dose of more than 0.5 mg. will lead after a few days to considerable fluctuations in the prothrombin times, owing to the cumulative effect of the drug. Once the approximate daily maintenance dose has been ascertained and the prothrombin times have been steady for three or four days, a good approximate guide to any further changes in the maintenance dose which may be necessary to maintain a steady unfluctuating prothrombin time is not to alter the amount of the dose by more than 5%.

To determine the appropriate small variations in dose at this stage, bearing in mind the cumulative effect of anticoagulants, it is essential not just to consider the effect of a single dose on the prothrombin time the following day. A much clearer picture of the exact daily maintenance requirements of any anticoagulant will be obtained if the treatment is assessed over, say, a three-day period. By taking such a three-day period the full cumulative effect of small changes in dosage in the region of 5 to 10% can be readily seen and the exact daily maintenance requirements easily ascertained with a minimum of blood tests.

Ease of Control

Warfarin sodium is a remarkably easy drug to control, as the response to a given dose can almost invariably be reliably predicted. In this trial 25-mg., 10-mg., 5-mg., and 3-mg. tablets were made available. The 25-mg. tablet was used for initial dosage and the 10-mg., 5-mg., and 3-mg. tablets for maintenance therapy. For the initial doses of 35 to 50 mg. advised here, the 25-mg. tablet is unnecessary. To prescribe small variations in dose of the order of 5% the strength of tablet available is, however, of great importance. Indeed, to-day, with several good anticoagulants available, what makes one anticoagulant much easier to control than another is often the ease and convenience with which very small variations in dose may be prescribed.

The overall average maintenance dose of warfarin sodium is about 9 mg. and a 5% variation of this amount about 0.5 mg. In assessing the exact daily requirements, as mentioned earlier, it is essential to take a three-day period so that the full cumulative effect of the drug on the prothrombin times can be taken into account. For warfarin sodium one-half of a 3-mg. tablet, more or less, each three-day period, would give the necessary 0.5-mg. variation a day. A tablet strength exceeding 3 mg. makes it much more difficult to prescribe small variations in dose. To cater for initial doses of 35 to 50 mg., and for those patients who need daily maintenance doses of 12 mg. or more, a second tablet of 5 to 6 mg. or so is necessary. With two such strengths of tablet (3 mg. and 5 mg.) accurate assessment of dosage can be quickly and easily made. For long-term therapy a tablet strength of approximately 3 mg. is essential.

Conclusions

Warfarin sodium was used in the treatment of 175 patients with thrombo-embolic diseases. It is a rapidly acting drug, and 95% of all patients reached a therapeutic prothrombin time in 36 hours. With daily doses of the drug just sufficient to maintain a therapeutic prothrombin time the duration of action is approximately 36 hours. However, in large doses warfarin sodium has a very sustained effect, with a duration of action up to four to five days. It is important, therefore, to avoid large doses. The usually recommended initial dose of 60 to 75 mg. proved far too much in this series; 35 to 50-mg. doses proved perfectly adequate for initial therapy, and it is inadvisable to exceed 50 mg. as an initial dose. The overall average maintenance dose was 9 mg., and 80% of all patients were maintained on daily doses between 5 and 15 mg.

Warfarin sodium proved extremely easy to control, and it probably ranks with phenindione as one of the two best anticoagulant drugs available for short-term therapy. Initial experience with warfarin sodium shows that it is also a very useful anticoagulant for long-term therapy. Great care must be taken in prescribing the anticoagulant to allow for the very definite cumulative effect of the drug. In this respect warfarin sodium resembles in its action that of phenylpropylhydroxycoumarin, which has proved a very reliable anticoagulant for long-term therapy.

To obtain the best results with warfarin sodium it is necessary to have available a strength of tablet with which to prescribe variations in dose of 0.5 mg. easily and quickly. It is considered that scored 3- and 5-mg. tablets would be ideal.

Thanks are due to Dr. Samuel M. Gordon, of Endo Laboratories Inc., New York, for his most helpful advice and for making available the various strengths of coumadin tablets which I have used, and also to Evans Medical Supplies Ltd. for supplying warfarin sodium ("marevan") in 3 mg. and 5 mg. strengths.

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STAPHYLOCOCCUS AUREUS TYPE 80 AND HUMAN INFECTIONS IN UGANDA

BY

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The differentiation of cultures of staphylococci by phage-typing has contributed notably towards an understanding of the epidemiology of staphylococcal disease. As well as being of value in tracing infections to particular sources, the method has provided useful information about the distribution and spread of strains of different phage types. Studies of strains isolated from healthy persons and hospital patients have shown that some phage types occur more frequently than others in certain environments, while an association between phage type and antibiotic resistance has been widely observed.

The high prevalence of antibiotic-resistant strains of phage group III in hospital infections is of special clinical interest (Blair and Carr, 1953; Rountree, 1953; Jackson, Dowling, and Lepper, 1954; Knight and Holzer, 1954). Again, some phage types seem to spread readily, while others are associated with infections possessing distinctive features. Examples of these tendencies are the recovery of type 52A strains from

hospital infections of newborn infants (Barber, Hayhoe, and Whitehead, 1949; Colbeck, 1949) and of type 71 strains from impetigo contagiosa (Spittlehouse, 1955; Parker, Tomlinson, and Williams, 1955; Barrow, 1955) and pemphigus neonatorum (Gillespie, Pope, and Simpson, 1957). Staphylococci of phage type 80 have recently been found in serious infections, often of an epidemic nature; this report is concerned with the relatively high incidence of such strains in a series of cultures from Uganda.

Infections caused by *Staphylococcus aureus* type 80 were first encountered in Australia in 1954 (Rountree and Freeman, 1955; Clarke, McGeoch, and Sippe, 1956). Strains of this type were lysed by a phage adapted from typing phage 52A, the adapted phage being designated typing phage 80. They have been isolated from an epidemic of furunculosis among hospital workers and from many outbreaks of neonatal infection in hospitals throughout Australia. Skin lesions were numerous and some infants developed pyothorax. Nearly all strains were penicillin-resistant and appeared to be of relatively high virulence.

Since 1955, type 80 strains have been identified in Europe. They have been observed in several extensive hospital outbreaks in Britain (Anderson and Williams, 1956). Ruys (1957) has remarked upon their prevalence in the Netherlands, where they have been recovered from a considerable proportion of infective conditions. As in Australia, the strains were generally penicillin-resistant, and Bijlmer (1957) recovered them from some fatal infections.

In view of the association of type 80 staphylococci with virulent infections in Australia and Europe, it was of interest to find that about 40% of 248 strains recently sent to us from East Africa belonged to this type. The strains had been recovered from pus and other specimens collected from patients at two hospitals in Uganda. The results of phage-typing and antibiotic sensitivity tests are given below.

Materials and Methods

Between November, 1955, and March, 1957, batches of staphylococci isolated at the Central Laboratory, Kampala, were sent to us at intervals of a few months for study of their lysogenic properties. These strains, which were unselected, came from routine cultures of material collected in the wards and out-patient departments of two general hospitals at Kampala; one (Mulago Hospital) served Africans and the other (Nakasero Hospital) served mainly Asians and Europeans. Strains were tested for coagulase production in tubes with 1/5 dilution of human plasma. Coagulase-positive strains were phage-typed by the method of Williams and Rippon (1952) and tested for antibiotic sensitivity on agar plates by means of "sentest" tablets.

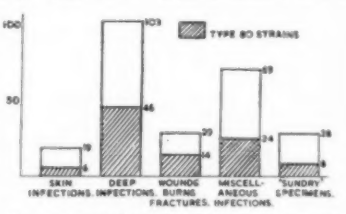
Phage-typing

A total of 248 strains proved to be coagulase-positive. They all produced yellow pigment and were taken to be *Staph. aureus*. Table I gives the numbers of strains belonging to the various phage groups and to phage type 80 which were recovered from specimens received from each hospital.

TABLE I.—*Phage-typing of Strains of Staph. aureus from Two Kampala Hospitals*

	Group I		Group II	Group III	"Mixed" Groups			Not Typable	Total
	Type 80	Others			I–III	II–III	III–IV		
Mulago Hospital ..	73	23	13	22	19	1	1	9	161
Nakasero Hospital ..	25	16	12	22	2	0	0	10	87
Total ..	98	39	25	44	21	1	1	19	248
	40%	15%	10%	18%	8%	1%		8%	100%

The proportions of type 80 strains derived from Mulago and Nakasero Hospitals were thus 73/161 (45%) and 25/87 (29%) respectively. Type 80 strains were by far the commonest single phage type in the whole series; as shown in the Chart, they were frequently recovered from all sources except "sundry specimens" (sputa, urines, blood cultures, swabs from the upper respiratory tract). They made up 45% of 103 strains from "deep" infections which included 80 abscesses (23 classed as "pyomyositis," 6 cases of osteomyelitis, and 4 of empyema); 48% of 29 strains from wounds, burns, and fractures; and 35% of 69 strains from miscellaneous pyogenic infections which could not be allocated to the "skin" or "deep" category on the clinical data.



Proportions of type 80 strains among cultures from different sources.

The incidence of type 80 infections among patients of different races was 45% (73 out of 161) in Africans, 30% (10 out of 33) in Asians, and 28% (15 out of 54) in Europeans.

When type 80 strains were tested for lysogenicity, it was found that 9 out of the 98 strains released phage which lysed the remaining strains of this type. Except for these nine strains, no other type 80 strain yielded phage which could be detected on any of the indicator strains used. A non-typable strain released a phage which formed plaques on all type 80 strains; strains which were made lysogenic with this phage became resistant to typing phage 80.

Antibiotic Sensitivity

The results of tests for antibiotic sensitivity are given in Table II. The proportion of penicillin-resistant strains was highest among staphylococci of phage groups I (90%) and III (64%). Strains resistant to both penicillin and streptomycin were much more frequent in group I, where 41 strains (30%) belonged to this category.

TABLE II.—*Sensitivity of 248 Strains of Staph. aureus to Antibiotics**

	No. of Strains	No. of Strains Resistant to						No. of Strains Sensitive to PSATCE
		P	S	A	T	C	E	
Group I { Type 80 ..	98	95	30	3	3	0	0	3
Group I { Others ..	39	28	15	0	0	0	0	10
Group II	25	2	0	0	0	0	0	23
,, III	44	28	7	6	6	4	0	16
"Mixed" groups ..	23	3	0	0	0	0	0	20
Not typable ..	19	6	3	1	0	0	1	9
Total ..	248	162	55	10	9	4	1	81

* P = Penicillin. S = Streptomycin. A = Chlortetracycline. T = Tetracycline. C = Chloramphenicol. E = Erythromycin.

Table II shows the extent of penicillin resistance in strains of each group and of type 80. Resistance to both penicillin and streptomycin was present in 28% (27 out of 98) of type 80 strains.

Discussion

Information about the phage types of staphylococci which are responsible for human infections in tropical Africa seems to be lacking. This series of strains from Uganda is of interest in that the predominant phage type (type 80) is one which has displayed marked pathogenicity in Australia and Europe. Type 80 strains made up 40% of the series, the remainder showing a wide range of differing lytic patterns. Among the staphylococci of phage group I, which

outnumbered those of group III by more than 3 to 1, the proportion of type 80 strains was 72%.

Type 80 strains were associated with a variety of infective conditions, some of which may have been acquired in hospital. The proportion of type 80 strains among staphylococci recovered from different sources ranged from 32% (skin lesions) to 48% (wounds, burns, and fractures). There was no indication that type 80 infections occurred as part of a definite "outbreak"; between 20% and 60% of each of five batches of strains received over 17 months were of this type.

The high incidence of penicillin resistance among type 80 strains accords with experience elsewhere. These staphylococci, possessing a distinctive lytic pattern and a marked insensitivity to penicillin, seem to form a group of considerable pathogenic potentiality. From the lysogenic standpoint, the 98 strains classed as type 80 were not homogeneous, nine strains liberating a phage to which all the remaining type 80 strains were sensitive. It would appear that type 80 strains, like type 52A strains, possess properties which favour their growth and spread in man; further data relating to their prevalence among the patients and staff of hospitals in tropical Africa would be valuable.

Summary

Strains of *Staph. aureus* type 80 formed 40% of 248 cultures of coagulase-positive staphylococci recovered from patients suffering from various infective conditions in Uganda. Type 80 strains were by far the commonest phage type in this series, and nearly all (97%) were penicillin-resistant. Strains of this type appear to be responsible for serious infections; their prevalence among hospital workers deserves study.

We are indebted to Dr. A. B. Raper and Dr. E. C. Buck for strains of staphylococci, and to Dr. R. E. O. Williams and Dr. Joan E. Rippon for typing phages and helpful information.

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Speaking at the conference of the National Society for Clean Air on October 1, the Minister of Housing and Local Government, Mr. HENRY BROOKE, said that on the industrial side we ought to see a substantial improvement within the next five years or so. The period allowed by the Clean Air Act for alterations to plant expired in the middle of 1963. During this time all the necessary improvements to furnaces and boilers would have to be carried out—the fitting of mechanical stokers, and the provision of instruments for observing and checking smoke. There ought also to be a steady growth in the fitting of dust and grit arrestors to furnaces. In the processes which came under the Alkali Act there should also be improvements coming along by then. For instance, in the gas and electricity and pottery industries the process of shutting down older works would have gone yet a stage further; and it was the older works which so often were responsible for the most smoke.

Medical Memoranda

Arteriovenous Fistula Following Blunt Trauma

Recently we had occasion to treat an arteriovenous fistula which seemingly resulted from a non-penetrating wound and had no features to suggest a congenital origin. A review of the modern literature failed to reveal a similar fistula following trauma by a blunt instrument which did not penetrate the tissues.

Post-traumatic arteriovenous fistulae and false aneurysms are a frequent complication of penetrating wounds in war. In civilian life congenital arteriovenous fistulae are often encountered, but an arteriovenous fistula or false aneurysm following a non-penetrating wound is a rarity. The case under discussion represents another form of aetiology of arteriovenous fistulae which is uncommon enough to be of interest to others.

CASE REPORT

A man aged 21 was referred because of a history that he had been struck on the left temple by a hockey ball. He was not rendered unconscious, but noted the immediate formation of a swelling at the area of impact, which in three to four hours' time had assumed the size of half a goose's egg. The skin was not broken nor was there any bleeding. On the evening of his injury he noticed a "buzzing" sensation just in front of the left ear. Within the next few days the swelling disappeared, but he continued to be aware of a whirring sensation in the area of trauma, noted when recumbent with the head turned so that the left side was down. It was only the persistence of this annoying buzzing in front of the ear for four months that led him to seek medical attention. Close questioning failed to disclose any history of previous penetrating injury in the left temple area or any skin lesion such as a capillary naevus or angioma.

On examination the pulse rate and volume were normal; blood pressure 130/80 mm. Hg. The significant physical findings were limited to the left temporal area, where there were several conspicuous subcutaneous veins anterior to the ear. Light palpation disclosed a systolic thrill, and on auscultation there was a continuous murmur with a crescendo in systole. Firm pressure upon the superficial temporal artery abolished the bruit; lighter pressure over the dilated veins caused marked engorgement of the veins of the scalp, and the bruit again disappeared. In view of the history and findings a diagnosis of post-traumatic arteriovenous fistula of the superficial temporal artery and vein was made, and at operation the superficial temporal artery and vein were exposed and found to have a fistulous communication. Accordingly a quadruple ligation was performed with excision of included vein, artery, and fistula. Recovery was uneventful and the patient has noted no further symptoms.

COMMENT

The pathogenesis of the fistula presents the point of major interest in this case. The patient absolutely denied any abnormal prominence of the veins of his temple, peculiar vibrations, or whirring prior to the traumatic episode. In fact, there was nothing to suggest that he might have had a small arteriovenous fistula which was enlarged by the blow. It seems most likely that the two vessels lying in close proximity must have been ruptured partially by the severe force, forming a communicating haematoma between them. A vascular channel subsequently developed and remained patent after resorption of the confined haematoma. Owing to the anatomy of the temporal region the haematoma was enclosed in a small space limited by the epicranial aponeurosis and its attachments to the zygomatic arch. There was little chance of dissection of the extravascular blood such as would be allowed in the areolar tissues surrounding vessels in most parts of the body.

Large haematomas are, of course, frequent after blunt trauma, and it is surprising that more arteriovenous fistulae do not develop. As stated above, a special anatomical situation must necessarily exist in which vessels rupture into a confined space. The open venous channel affords the line of least resistance for the blood under arterial pressure, rather than diffusion of the blood into the tissues such as normally occurs. If the vascular shunt is maintained the channel will gradually become organized and lined with endothelium, and an arteriovenous fistula will have been established.

I thank Professor Sir James Paterson Ross for allowing me to publish this case and for advice and help in the preparation of this paper.

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Empyema Caused by Pasteurella septica

In the fatal case of empyema described below, *Pasteurella septica* was isolated both during life and after death. This organism is not infrequently isolated from the upper respiratory tract in man, but its importance as a pathogen is extremely difficult to assess. In Britain it has only twice been incriminated as the causal agent in infection of the respiratory tract—once in a case of sinusitis (Bartley and Hunter, 1947), and once as the cause of repeated exacerbations in a case of bronchiectasis (Cawson and Talbot, 1955). Elsewhere, cases of empyema caused by *P. septica* have been described, but only nine reports can be regarded as adequately substantiated by the bacteriological findings.

Case Report

A 76-year-old woman was admitted to hospital on December 20, 1955, complaining of pain in the right hypochondrium and vomiting for three days. On examination she was dyspnoeic and pyrexial—99.2° F. (37.3° C.). Right subcostal tenderness and guarding were present, but there were no other abnormal findings. She had a remittent pyrexia for two days, and then developed grunting respirations and a rust-coloured sputum. Signs of a right lower-lobe pneumonia with pleural effusion were confirmed by *x*-ray examination. A blood count revealed a leucocytosis of 22,900/c.mm. Treatment with penicillin (crystalline) intramuscularly, 500,000 units six-hourly, produced temporary improvement, but after two more days signs of congestive cardiac failure developed. There now seemed to be an effusion only at the right base, and, in view of the continued deterioration, chest aspiration was performed. A small volume of blood-stained pus was withdrawn, which contained numerous polymorphonuclear leucocytes and minute Gram-negative coccobacilli. Culture yielded a heavy pure growth of *P. septica*. Penicillin was instilled into the loculus entered, and chlortetracycline was given orally, but in spite of all supportive therapy the patient became increasingly feeble, dying on January 16, 1956.

Necropsy Findings.—Necropsy was performed four hours after death. A fibrino-purulent pleurisy involved the lower lobe of the right lung. In the right costophrenic recess there was a collection of 50 ml. of thick yellow pus, walled off by dense fibrous tissue. No gross consolidation was detected in the lungs, but histological examination showed the right lower lobe to be the site of an organizing pneumonia. Other positive findings were confined to the kidneys, which were contracted and coarsely scarred, and the large intestine, which presented an appearance compatible with a uraemic colitis. Cerebrospinal fluid taken at necropsy gave a urea level of 322 mg./100 ml. A specimen of the empyema pus produced, as before, a heavy growth of *P. septica*. The organism was not recovered from material taken from the lungs, trachea, fauces, liver, spleen, heart blood, or cerebrospinal fluid, nor did Gram stains on all organs sectioned show any evidence of Gram-negative coccobacilli. The final post-mortem diagnosis was "chronic pyelonephritis, pneumonia with empyema occurring as a terminal event."

Bacteriological Findings.—In films prepared from the empyema pus the organism was seen to be a coccobacillus measuring approximately 1.5 by 0.5 μ. Bipolar staining was easily demonstrable, but capsules were not seen. The organism was Gram-negative and non-acid-fast. Its cultural characteristics were typically those of *P. septica*. It grew easily on blood agar and on nutrient agar, but not at all on MacConkey's agar. Two notable features were a peculiar brownish discoloration produced on blood agar after 48–72 hours' incubation, and a semen-like odour given by cultures on this medium. Biochemical reactions were again typical, with the single but important exception of the production of acid from lactose. The antigenic structure and pathogenicity of the organism were investigated by Dr. G. H. Tee. He found it to be agglutinated to a titre of 1:5,120 by an antiserum prepared against a lactose-fermenting organism which had been isolated from a cat-bite and which appeared to be *P. septica*. He also inoculated two mice intraperitoneally with 0.1 ml. of an 18-hour broth culture of our organism diluted 1:100. Both mice died within 24 hours, and were found to have peritonitis with free fluid in the abdominal cavity. A pure growth of an organism with similar properties was recovered from their spleens. Finally the organism was tested against antibiotics, using a standard dried-disk technique; it was found to be sensitive to penicillin, streptomycin, chloramphenicol, the tetracycline group, and polymyxin, but resistant to erythromycin.

Comment

Two features in this case are noteworthy. First, it adds to the slowly accumulating body of evidence implicating *P. septica* as a definite potential pathogen in the respiratory tract in man. When Schipper (1947) reviewed human infections with *P. septica*, he divided them into two main groups—local infections due to animal bites, and infections, usually systemic, not obviously attributable to any direct cause. It seems to us, however, that cases of respiratory infection might well be separated from this second rather vague group, with consequently increased emphasis on their frequency and importance. The relatively large series of cases of bronchiectasis, including two complicated by empyema, reported by Olsen and Needham (1952) lends support to this view.

The second feature is of primarily bacteriological interest, and concerns the unusual property possessed by our strain of *P. septica* of producing acid from lactose. There is no published reference to a lactose-fermenting strain being isolated from man. However, such strains have often been described by veterinary workers (Jones, 1921; Rosenbusch and Merchant, 1939), and were referred to by Allin (1942) in a review of cat-bite infections. Moreover, Tee (1956, personal communication) has obtained from sputa several strains of lactose-fermenting organisms which otherwise seemed typically *P. septica*. There is therefore strong evidence that the production of acid from lactose is a property of certain not uncommon strains of *P. septica*, and that such strains may on occasion be pathogenic for man.

We are indebted to Dr. G. H. Tee for his invaluable assistance in carrying out the serological and pathogenicity tests; to Dr. C. S. S. Don for permission to publish the clinical details of the case; to Dr. A. Nicol for the necropsy report; and to Dr. R. W. Fairbrother for his advice and encouragement.

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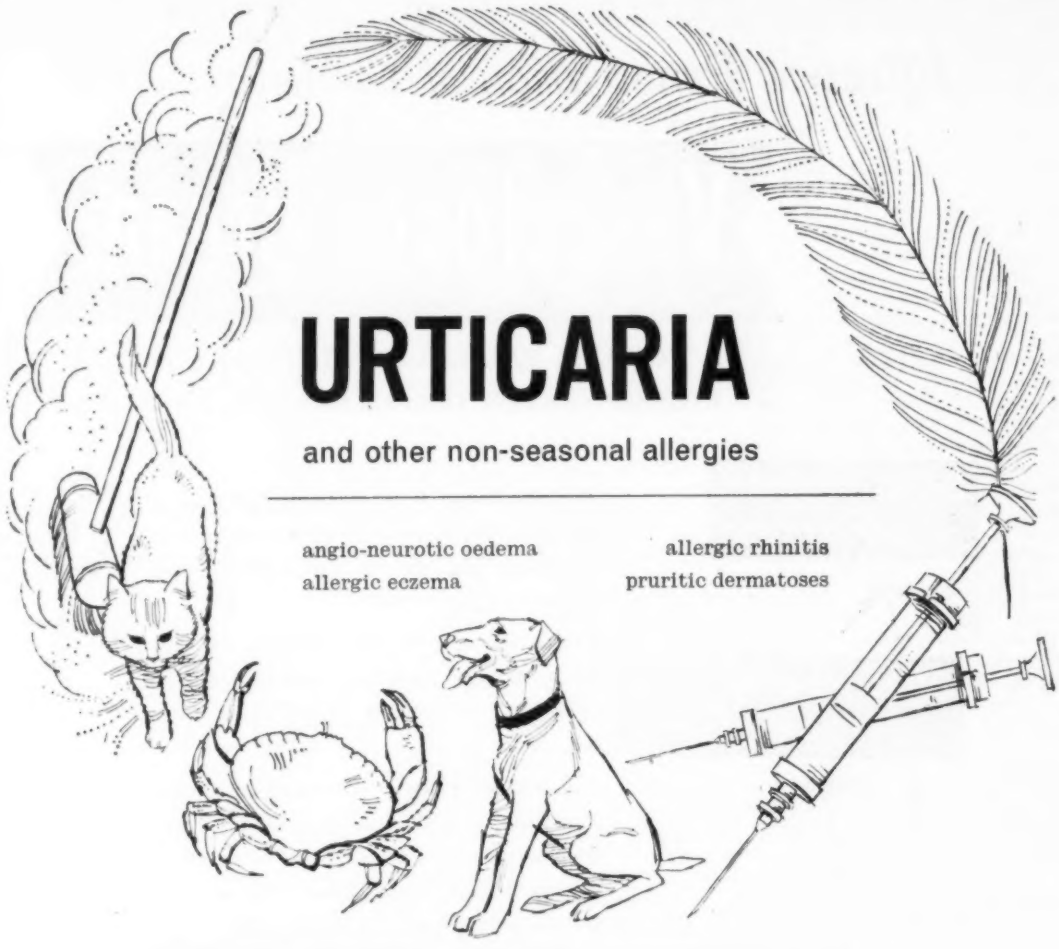

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Reviews

HYPERTENSION

High Arterial Pressure. By F. H. Smirk, M.D., F.R.C.P., F.R.A.C.P. (Pp. 764+xxxvi; illustrated. 75s.) Oxford: Blackwell Scientific Publications. 1957.

The recent recognition of Sir Frederick Smirk's contribution to medicine was well timed in relation to the publication of his most important work. In this monumental volume he describes in detail virtually all that a clinician could want to know about hypertension, and few have studied it clinically so exhaustively or treated it more successfully. The book is essentially clinical and will be appreciated most by those who have to look after the patients.

While a monograph of this size must be classed as a reference book—and there are, incidentally, some 2,500 references—it is very readable and has that desirable continuity so often lacking in books of multiple authorship. The first four chapters are concerned chiefly with the relationship or reaction of the blood pressure to environment, diet, somatotype, race, and daily activities, and constitute an excellent introduction. Chapter V, on the clinical manifestations of hypertension, is less convincing, but how unimportant these seem in relation to the whole! Known causes of hypertension, including psychiatric factors, are then considered in detail, and this is followed by chapters on the physiology of blood-pressure regulation and on experimental hypertension. All this leads up to the author's views on the pathogenesis of essential hypertension: very briefly he contends that all the clinical manifestations are the results of high pressure itself, however produced or maintained; that a wide variety of neurogenic and non-neurogenic factors may be responsible for the rise of pressure; and that certain mechanisms exist which tend to make hypertension self-perpetuating. It is interesting to reflect that quite independently almost exactly similar views have been expressed recently in relation to pulmonary hypertension after a very much shorter period of study.

Apart from a chapter on prognosis, the rest of the book (330 pages) is devoted to treatment. Far from engendering respect for such careful, complete, and detailed work, this elaborate therapeutic section has excited a curious reaction in some quarters: remarks such as, "What treatment that is any good requires 330 pages to describe?" and, "Devil's brew," illustrate this reaction. But it is both stupid and churlish to deny the value of this therapeutic section, because hypertension is not as well treated as it should be, and successful management demands close attention to detail and familiarity with the potency and side-effects of a fairly large range of hypotensive agents.

While many books have been written about hypertension, there is no other that provides so much practical information, and it is therefore highly recommended to all who have to deal with this common and troublesome condition.

PAUL WOOD.

HORMONES AND BREAST CANCER

Endocrine Aspects of Breast Cancer: Proceedings of a Conference held at the University of Glasgow, 8th to 10th July, 1957. Edited by Alastair R. Currie, B.Sc., M.B., F.R.C.P.Ed. Foreword by C. F. W. Illingworth, C.B.E., M.D., Ch.M., F.R.C.S.Ed., F.R.F.P.S. (Pp. 340+xvi; illustrated. 37s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1958.

This book deals with the proceedings of a conference held at the University of Glasgow from July 8 to 10, 1957, in which there were over 90 participants from Great Britain and other countries. This should not, however, deter the reader, because by skilful editorship Dr. A. R. Currie has managed to give the book a continuity which is rare in volumes of this kind. A discussion follows the reading of most papers. The first part deals with the clinical aspects of breast cancer, and the remaining three sections are on hormone studies and experimental pathology. In conclusion there is a comprehensive review of the work discussed at the conference, ably presented by Professor C. F. W. Illingworth.

During the last decade some interesting facts have been brought to light on the role of hormones in carcinogenesis. Not only have new hormones been recognized and isolated, but knowledge of the mechanisms which regulate these secretions has also been extended. It is therefore heartening to find that many of the discoveries which have been achieved in the laboratory are now applied clinically. This is especially true in the case of breast cancer, for it is now firmly established that the sex hormones of gonadal and adrenal origin play an important role in the development of breast cancer. Unfortunately at the present moment the role of the pituitary gland is less well understood, though one reads in this volume of promising researches on pituitary function which might have important clinical applications. Certain types of breast cancer, following application of endocrine therapy, undergo remission, and, even if the improvement is only of temporary duration, this in itself is a stimulating achievement. Recurrences of tumour growth after periods of remission following both gonadectomy and adrenalectomy suggest that the anterior pituitary may be capable of stimulating adrenal rests to secrete oestrogens to a degree sufficient to reactivate the neoplasm, or it may even be that the recurrence of some breast carcinomas is due to a pituitary hormone or hormones acting in addition to oestrogen. Clinical results following hypophysectomy without previous gonadectomy and adrenalectomy for patients with breast cancer suggest that this might be so. As Professor Illingworth rightly emphasizes in his concluding remarks, oestrogens may not be the only offenders in the induction of breast cancer. More research should still be done on the possible influence and sources of other hormones, such as progesterone and gonadotrophins, as well as prolactin and the growth hormone.

This volume is to be recommended particularly because it links together a vast mass of data on the endocrine induction and control of breast cancer in a way that can be appreciated by the medical practitioner and scientist alike. It is also a most useful book of reference for those interested in the general subject of hormones and cancer.

E. S. HORNING.

PSYCHOTHERAPY

Psychotherapy: A Modern Theory and Practice. By E. Lakin Phillips, Ph.D. (Pp. 334+xviii. 30s.) London: Staples Press Limited. 1957.

In a study on communication Ruesch and Bateson[1] note the remark of a Freudian, "The more experience I have in psychiatry the more convinced I become that it is impossible to verbalize what I do." It is indeed a characteristic of psychotherapists of all persuasions that they are unable to describe how their results are achieved, coupled with a certain reluctance to consider critically the efficacy of their efforts. This is an attitude which one cannot expect scientifically trained psychologists to tolerate, and, as they become interested in psychotherapy, a situation which obtains in the United States, so it is to be expected that they will examine the theories, assumptions, and results of psychotherapy in the same way as, say, intelligence or personality testing.

The author of this book notes, for example, that psychotherapists seem to get much the same sort of results though they hold very different theories and employ different methods. What effects the improvement in the patient—if, indeed, there is any improvement beyond that which would occur spontaneously—would seem to lie, not in the particular nature of the theories held by the individual psychotherapist, but in some other factor or factors common to all psychotherapy. It is obviously a matter of some interest and importance to consider these common factors, but this

[1] Ruesch, J., and Bateson, G., *Communication: The Social Matrix of Society*, Norton, New York, 1951.

is a task for which the clinician, engrossed with the particular aspects of his own brand of psychotherapy, is unfitted.

The author's attitude towards the critical study of psychotherapy is a most salutary one, whether or not one agrees with his views on the particular nature of psychotherapy which should be followed. He criticizes depth therapy on the grounds that it is fundamentally unsound, that its concepts are unnecessary, and that its duration is protracted because the psychotherapist is dealing with irrelevancies rather than tackling the present problems. He comes out in favour of a conflict theory and of a short-term directive psychotherapy consisting in bringing to the patient's notice his immediate conflicts which are responsible for his symptoms. On this basis he discusses the applicability of the work on experimental neuroses, much of which, however, he regards as naive. He attempts to evaluate the results of his therapy and claims that it is more effective than grubbing around in the unconscious for years; indeed, the whole concept of the unconscious comes in for sharp scrutiny.

The author devotes a chapter to the controversy between the monothetic approach—that is, the analytic approach in search of general laws which are statistically verifiable—and the idiographic or intuitive approach. He does not decry the intuitive approach, which would seem to be indispensable in dealing with particular problems ("no monothetist can tell what his wife would like for a Christmas present by applying the general laws of psychology"), and he regards the method of the clinician as that of adding an idiographic touch to the monothetic data he obtains from the patient.

Apart from the views expressed in this book, its main importance is that it emphasizes the lively nature of psychology in the U.S.A. Psychotherapy is in great need of a critical scrutiny of its basic assumptions and its *modus operandi*. Such a study is more likely to be made by psychologists than clinicians, and this book demonstrates the sort of contributions that psychologists can most valuably make to psychiatry. It is a book which should be read by all psychiatrists, not only for the views of the author on his short-term directive psychotherapy, but for the insight it gives as to how psychology might truly come to bear the relationship to psychiatry that pathology bears to medicine—still a very distant ideal.

A. W. Beard.

MODERN ENDOCRINOLOGY

Modern Trends in Endocrinology. Edited by H. Gardiner-Hill, M.D., F.R.C.P. (Pp. 298+x; illustrated. 65s.) London: Butterworth and Co. (Publishers), Ltd. 1958.

Dr. Gardiner-Hill is the doyen of English clinical endocrinologists, and those of us who have followed him must ever be grateful for the aura of respectability which he cast around a specialty which a quarter of a century ago was not quite "a profession for a gentleman." He re-emerges now as editor of what must be the most star-spangled of all books on endocrinology. The late Michael Todd hardly did better when he collected his cast for "Around the World in Eighty Days." To list the authors would be merely to name two dozen from amongst the most distinguished endocrinologists from the laboratories and wards of the English-speaking world. To pick out any from such a company may be unfair, but at the risk of being so I would say that no one (however learned) who treats thyroid diseases can fail to learn something from the masterly chapters by Dr. Rosalind Pitt-Rivers, Dr. E. E. Pochin, and Dr. G. C. Kennedy and Professor R. A. McCance.

Of course there are omissions which strike the eye. In a book called "Modern Trends" dated last October and containing five chapters on the thyroid it is surprising to find no reference to auto-immunization. The authors of the chapter on tests of thyroid function, by what was obviously a momentary lapse of memory, forgot to say that patients with goitres without thyrotoxicosis often have a great avidity for radio-iodine. There is no mention of the valuable part played by triiodothyronine in the control of patients with thyroid carcinoma. Dr. P. J. Randle, who writes with admirable clarity about diabetes mellitus, expressly excludes a discussion of the importance of the thyroid, obesity, and heredity, which is a pity. Space should have been found for the recent work of Kekwick and Pavan, who have succeeded in proving (what so many of us have long believed) that there are more things in heaven and earth than calories in the diet of the obese. And of course there are bound to be points of disagreement between any reviewer and any author, but reviewers are not, as once they were assumed to be, omniscient, and such matters are best left unnoticed unless a brick has been dropped large enough to be a stumbling-block. There are no such bricks here. Indeed, the only criticism which is likely to be general is that the book lacks balance. Though all parts are very good, the whole is less than their sum. The editor's answer, and a satisfactory one, is that this is not intended to be a textbook of endocrinology, but a series of essays planned to indicate some of the salients on the endocrine front. He says himself—and he should know—that the book "will be a helpful addition to the library of physicians, endocrinologists, postgraduates and others." I agree.

Raymond Greene.

SANCTITY OF LIFE

The Sanctity of Life and the Criminal Law. By Glanville Williams. (Pp. 319. 30s.). London: Faber Ltd. 1958.

Concealed behind the pedestrian title of this book lies a topical volcano bubbling with ideas founded on a profound substratum of legal and historical knowledge. You begin with a placid first chapter on the protection of human life. This investigates the medico-legal niceties of birth and death—when the unborn child can be considered as alive, and when in the light of resuscitative techniques you should be regarded as really dead. It deals with the associated problems of concealment of birth, child destruction, infanticide, and what is to be done about monsters. From this you pass to the topical and controversial—to the control of conception, to sterilization, to artificial insemination, to abortion, to suicide, and to euthanasia. Professor Glanville Williams examines each of these problems against its historical background and in its present social context. Lawyers and politicians, Protestants and Popes, come in for searching criticism. He reviews the law as it is in England and in the American jurisdictions. On suicide, for example, he reminds us that the Christian attitude originates not from the Gospels or St. Paul but from St. Augustine's condemnation of the Circumcelliones. These cast themselves by the hundreds in ecstasy from lofty cliffs, for "to kill themselves out of respect for martyrdom is their daily sport." On eugenic sterilization he reminds us of Justice Holmes's observation in the United States Supreme Court in *Buck* v. *Bell*, decided in 1927, "Three generations of imbeciles are enough."

Not all will agree with all of Professor Williams's criticisms and suggestions for improvement; but this is a stimulating and instructive book which will give all but the most firmly closed minds considerable food for thought.

"A Barrister."

A second edition of Mr. J. C. Adams's *Outline of Orthopaedics* has appeared only two years after the first (reviewed in this *Journal* on May 12, 1956, p. 1089). This book, intended primarily for senior students, gives an adequate outline of orthopaedic conditions and their management. It is published by E. and S. Livingstone, Ltd., Edinburgh (pp. 428, 300 illustrations; 35s.).

Professor Oliver E. Byrd, of Stanford University, has selected 254 articles from 78 journals to form the basis of *Health Yearbook, 1956* (pp. 278; London, Oxford University Press, 1957; 40s.). These articles "represent the research, experience, and opinion of approximately 300 authors, committees, organizations, and other groups in the fields of public health, medicine, and allied scientific areas," but only nine come from outside the United States, and none from foreign-language journals.

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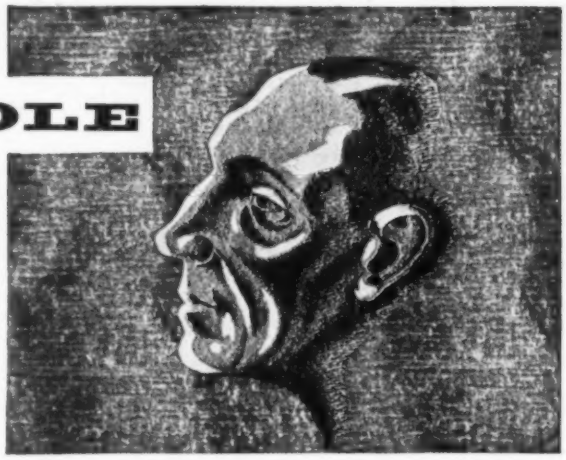

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5	£3 —	£2 15s.	£2 10s.	£2 5s.	£2 —	£2 —
6	£3 12s.	£3 6s.	£3 —	£2 14s.	£2 8s.	£2 8s.
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BRITISH MEDICAL JOURNAL
LONDON
SATURDAY OCTOBER 11 1958

FAINTING

A wide variety of conditions may precipitate fainting. It may occur after prolonged standing in the erect posture, sympathectomy, violent coughing, or the administration of ganglion-blocking drugs and nitrites, and it may be a complication of haemorrhage or pregnancy. Arterial hypotension is a constant feature of it. Now Professor E. P. Sharpey-Schafer and Drs. C. J. Hayter and E. D. Barlow show in an article at p. 878 this week that severe hypotension is not uncommonly precipitated by fear before the administration of nitrous oxide for dental extraction. Nausea caused by apomorphine was also found to lead to a similar vascular reaction.

Since arterial pressure is a product of total peripheral resistance and cardiac output, it follows that acute hypotension is due to a profound fall in one or both of these factors. The normal slight fall in venous filling pressure and cardiac output which occurs with a change to the upright posture in man is balanced by vasoconstriction; this "baroceptor constriction" has been observed in the vascular reactions accompanying squatting and performing the Valsalva manœuvre.[1-3] Fainting occurs when normal vascular reactions are inadequate and fail to maintain arterial pressure above some 50 mm. Hg. The constituents of the faint reaction, apart from the hypotension and resulting syncope, are independent of the cause, and include sudden bradycardia, pallor, sweating, and hyperpnoea, suggesting that the whole is a reflex phenomenon. Sudden vasodilatation, as shown by an increase of blood flow in the forearm, has been observed in fainting reactions accompanying haemorrhage,[4] tilting to the upright posture, spinal anaesthesia, and pregnancy.[5] Thus fainting will be enhanced in susceptible subjects by any factors which tend to increase vasodilatation, such as a warm atmosphere or thick clothing.

In most types of fainting there is evidence that inadequate filling of the heart, and consequently a reduced output and lower pulse pressure, is a crucial factor. The inadequate filling is due to venous pooling, which is why fainting is usually associated with the erect posture and is more likely to occur when the subject is in the lordotic position or has been standing for long. In pregnancy venous pooling is probably due to partial occlusion of the inferior vena cava by pressure of the gravid uterus.

Nitrites readily produce faintness because they cause venous dilatation as well as arteriolar relaxation. Venous pooling may be stopped by an anti-gravity suit, which thus prevents syncope.[6] Diminished filling of the right atrium is also an important factor in the mechanism of cough syncope.[7] Professor Sharpey-Schafer and his colleagues now suggest that the whole faint reflex may be initiated from afferent nerves stimulated by a relatively empty heart, this being caused not only by venous pooling but by vigorous systolic emptying owing to emotional stimulation. This ingenious hypothesis explains the strange absence of faint reactions in patients with congestive heart failure, when a residue of blood remains in the ventricles in diastole.

In a rare form of idiopathic postural hypotension there is syncope on standing, anhidrosis, and impotence.[8] These are the result of a central paralysis of vasoconstriction, and the effect is similar to that caused by extensive sympathectomy or an overdose of ganglion-blocking drugs. In these conditions syncope may occur before the full picture of vasovagal fainting develops; unconsciousness may supervene without bradycardia. However, the contributions of Sharpey-Schafer and others have shown that, apart from minor differences in degree of vascular reaction, in all forms of fainting the final mechanism is similar. There is sudden vasomotor failure in conjunction with reduced filling of the heart. The only homoeostatic feature of the reaction appears to be final collapse from the upright position, which leads to restoration of the venous filling pressure.

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INFECTIOUS MONONUCLEOSIS

Infectious mononucleosis, or glandular fever, is still a baffling disease. It is presumed to be a viral infection, though no causal organism has yet been found. A. Nyfeldt,[1] C. A. Pons and L. A. Julianelle,[2] and R. A. Webb[3] all thought that *Listeria monocytogenes*, a Gram-positive motile bacillus occurring naturally in rodents and ruminants, was the likely aetiological agent. *L. monocytogenes* is being found with increasing frequency in human infections,[4 5 6] and B. H. Chaiken and D. T. Michaud[7] report a case of infectious mononucleosis from which this organism was

isolated in 6 out of 8 blood cultures: the heterophil antibody titre was 1:448. But in the majority of cases *L. monocytogenes* has not been isolated, nor have positive agglutinins appeared. It seems possible that this is a syndrome with more than one cause. K. F. Girard and E. G. D. Murray[8] summarized the evidence in favour of a viral cause and of the view that *L. monocytogenes* was responsible, and suggested that the heterophil antibody was not directly produced by either organism but by some other non-specific immune mechanism set in motion by the affected lymphatic or liver tissue and by alteration in serum globulin. D. A. Goldthwait and J. W. Eliot[9] regard infectious mononucleosis as a disease presenting the triad of lymphatic hyperplasia, circulating abnormal lymphocytes, and the appearance of heterophil antibodies that are absorbed by ox red-blood cells but not by guinea-pig kidney. Heterophil antibodies of this pattern are generally regarded as occurring only in infectious mononucleosis,[10] and absorption tests are therefore essential in assessing the significance of a positive Paul–Bunnell reaction.

A. Bernstein,[11] in a comprehensive review, suggested that a negative Paul–Bunnell test almost excluded a diagnosis of glandular fever. C. E. Bender[12] was of a similar opinion, but pointed out that in certain forms, notably the "febrile" type and those cases with neurological manifestations, heterophil antibodies appear only in the later stages or even in convalescence. A rising titre of antibody is stronger evidence of the disease than an arbitrarily chosen level such as 1:64[13] or 1:56.[12] S. Leibowitz[10] originally regarded a positive Paul–Bunnell test as "almost an absolute yardstick of infectious mononucleosis": in 1956 he revised his opinion and said that "the validity of the diagnosis of infectious mononucleosis in sero-negative cases still remains to be established with certainty and will continue in some doubt until the aetiological agent is identified and an unquestioned diagnostic test results." In a field survey of 498 cases suspected on clinical grounds to be cases of glandular fever F. G. Hobson, B. Lawson, and M. Wigfield[14] found 242 had a positive Paul–Bunnell reaction, 100 were negative to the test but showed haematological evidence of the disease, and 156 had illnesses due to other conditions. It was not possible to differentiate sero-positive and sero-negative cases on purely clinical grounds except in retrospect, but the former tended to be more severe, while, though infectivity was low in both groups, the latter appeared to be the more infectious. There were notable differences in the two groups in seasonal onset and in the age and sex incidence, and glandular-fever cells were found to persist twice as long in the cases with a positive Paul–Bunnell reaction. The authors' conclusions supported the findings of S. Shubert and his colleagues[15] that sero-negative cases should be regarded as examples of a different disease. More detailed investigation of sero-negative cases is clearly required.

Serological surveys for toxoplasma antibodies in Britain[16 17] and in America have shown that by adult life between one-quarter and one-half of the entire population have become infected,[18] while the close resemblance of some cases of acquired toxoplasmosis to infectious mononucleosis has often been noted.[19 20] M. Bateman[21] has reported three cases in which an initial diagnosis of infectious mononucleosis had been made but subsequent Paul–Bunnell tests were negative and serological tests for toxoplasmosis were positive. In a more recent survey of 30 cases of toxoplasmosis in Sheffield, J. K. A. Beverley and C. P. Beattie[22] report that four were proved by isolation of the parasite and the remainder showed significantly high antibody titres. While lymphadenopathy appeared to be the commonest manifestation, the severity and duration of the illness varied enormously; five of their patients were never really ill, whereas in others the illness dragged on for months. All had negative Paul–Bunnell reactions. It is clear, therefore, that routine investigation for toxoplasma antibodies should be made both in cases resembling infectious mononucleosis with negative Paul–Bunnell tests and in cases of pyrexia of unexplained origin.

Evidence of widespread visceral disease in infectious mononucleosis has accumulated in recent years. Hepatic, cardiac, or neurological symptoms may predominate. Jaundice is a well-known development in proved cases (Leibowitz[10] found it in 28% of his series of 25 cases), but R. S. Nelson and J. H.

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Darragh[23] have shown by serial liver biopsies that non-icteric hepatitis is present in most cases. L. E. Rennie and F. Wroblewski[24] found that alterations in serum glutamic pyruvate transaminase (S.G.P.-T.) reflected most sensitively the presence and extent of hepatic infection, while the subjective manifestations of the disease appeared to coincide with the S.G.P.-T. levels, suggesting that fluctuations and variations in the symptoms of the disease might be explained in part by the amount of hepatic inflammation. B. H. Webster,[25] in a report on five cases of infectious mononucleosis—confirmed by increasing absorption titres of heterophil antibody with beef cells—which showed electrocardiographic as well as clinical evidence of severe cardiac complications, believes that the heart is more often affected than is generally suspected. D. M. Roseman and R. M. Barry[26] describe what they consider to be the eighth reported case of acute pericarditis occurring in association with infectious mononucleosis, and it is noteworthy that the signs of pericardial inflammation preceded those of mononucleosis by one week. Neurological complications of infectious mononucleosis are being reported with increasing frequency. Leibowitz[10] suggests that in the majority of cases the symptoms become manifest in the first to third weeks but that the clinical picture may be confusing; he noted that in the 71 cases recorded in the literature the mortality rate was 11%. E. P. Frenkel and his colleagues[27] have claimed good results with steroid therapy.

In the absence of notification the incidence of the disease cannot be calculated, but in common with some other viral infections it seems to be on the increase, and in semi-closed communities like the Army may be as common as infectious hepatitis and poliomyelitis. So varied is the symptomatology and mode of onset that infectious mononucleosis should be kept in mind in any infection of unexplained origin. The development of exudative tonsillitis after a variable period of febrile disturbance with malaise and possibly lymphadenopathy is one of the commonest patterns of the disease; while macular rashes, clinically indistinguishable from rubella, are often seen. The study of a blood film is thus an indispensable procedure in all such cases. Many references have been made to the enanthem of glandular fever,[28–34] and F. I. Caird and P. R. Holt[35] have made a detailed study of this phenomenon. They describe five types of lesion, the most important being multiple pin-point petechiae at the junction of the hard and soft palate. Red macules, linear macules, white macules, and vesicular lesions may also be seen. Caird and Holt maintain that such lesions are not generally found in diseases which infectious mononucleosis may simulate and may therefore prove helpful in a diagnosis which so often remains in doubt until the results of the Paul–Bunnell test are known. Much more might be learned about the aetiology and epidemiology of this infection if it was made notifiable, at least temporarily, in areas where the incidence is believed to be high.

WAITING FOR DOCTOR

To a patient already worried about his ill-health a long wait in the out-patient hall can seem uncommonly irksome. He may be suffering loss of earnings as a result of it, or the housewife may have trouble over getting her children looked after. It can be no surprise if they, like Marvell, are sometimes obsessed with the thought of "time's wingèd chariot hurrying near." Marvell was addressing his mistress, not his doctor (and hence in verse), but many people do find it a frustrating experience to fidget about for an hour or more in strange company waiting for their slightly alarming turn to come before the doctor. A number of investigations have by now been carried out into the various causes of long waits at the hospital clinic; a considerable literature on it has appeared; and last week a further contribution, partly reviewing previous work but adding fresh observations, was published by the Ministry of Health.[1] "Waiting in the clinic before seeing the doctor," says the report, "is the most frequent and most irritating cause of complaint."

As the report recognizes, many kinds of disturbance can upset the smooth running of an appointments system. The authors found that on the average about 10% of patients booked do not attend (though some give warning), and, though most patients come early, "there are often enough late comers to jeopardize the efficiency of an appointments system." The doctors in charge of the clinic may themselves be late, or have to leave suddenly to deal with an emergency, or to go off for a few minutes to consult a colleague. Again, the length of each consultation may vary enormously. To the statistician—and most studies of these problems have been executed by statisticians—these problems appear as measurable variables which, after some technical processing, can provide data from which to deduce the framework of a scheme. An appointments system may thus be constructed by which, for example, in 19 out of 20 successive out-patient sessions not more than 5 out of 100 patients would, on the average, have to wait more than one hour. The objective recommended in this report is that 75% of patients should be seen within half an hour of their appointment time, and that no more than 3% should have to wait over an hour.

[1] *Out-patient Waiting Time*, Hospital O and M Service Reports. H.M.S.O., 1s. 3d.

studied. Yet despite all the cases now recorded, and the work involved in their investigation, the aetiology of Marfan's syndrome remains unexplained.

PULMONARY TUBERCULOSIS AND PEPTIC ULCER

Pulmonary tuberculosis occurs more frequently in patients, especially men, after partial gastrectomy than in the general population.[1-4] This finding has been confirmed by J. A. Balint in a recent survey of mortality in a follow-up of 2,413 patients after gastrectomy.[5] The higher incidence of tuberculosis in men than in women after gastrectomy is due to the fact that the majority of men have this operation before they reach the most dangerous age for phthisis (55–65 years), while women have already passed what is for them the most dangerous age (20–30 years) before the operation.

Some workers have claimed that pulmonary tuberculosis is more prevalent among patients with peptic ulcer not treated by operation,[6 7] but others have disagreed with this view.[8-10] Balint in his survey examined the incidence of tuberculosis among 1,886 patients with peptic ulcer seen at the Central Middlesex Hospital during 1953–5 inclusive, and found no significant difference between this and the incidence in all other outpatients seen during the same period. However, his patients were new cases of peptic ulcer and therefore mainly of recent onset.

The increased incidence of tuberculosis after partial gastrectomy has been most commonly attributed to malnutrition,[11-14] yet there is much evidence that nutrition after gastrectomy is not usually severely impaired.[5 15-17] Furthermore, it has been shown that tuberculosis is just as likely to develop in patients whose partial gastrectomy is a success as in patients with bad results.[1 18] D. M. Kissen[19] has recently suggested that the increased prevalence of tuberculosis among patients with peptic ulcer has a psychological origin. While many doctors would agree that emotional disturbances often lead to recrudescence of ulcer symptoms, there is still much doubt about their significance in the aetiology of peptic ulceration. Other factors are known to be of importance in determining the increased incidence of tuberculosis in ulcer subjects. One of these is social class. W. R. S. Doll and colleagues[20] have shown that gastric ulcer is much more common in social class V than in social classes I and II. Tuberculosis is also more common in the lower social classes. Again, C. R. Lowe[21] has shown that there are an excessive number of heavy smokers among adult patients with pulmonary tuberculosis, while Doll and colleagues[22] have shown that peptic ulcer is more common in smokers than non-smokers. Thus smoking may be another important factor in the development of tuberculosis in patients with peptic ulcer.

Firm evidence of an increased incidence of pulmonary tuberculosis among patients with peptic ulcer is at present lacking, except that the incidence after partial gastrectomy is undoubtedly higher. Balint has calculated that cases of tuberculosis arising after partial gastrectomy may account for 5–10% of all new notifications of pulmonary tuberculosis in men. The explanation for this increased incidence appears to lie in the social class of the patients (mainly social class V), their heavy cigarette smoking, the age at which the operation is performed, and the slight malnutrition following partial gastrectomy.

AFTER DINNER

The medical schools are beginning the new session. Notable men make edifying speeches. And everyone dines. Usually the dinners are good, and also the wines. Everyone eats too much on these occasions. Surfeit is the rule. A medley of middle-aged men—with a few ancients around—sit uncomfortably with starched shirtfronts and become flushed and even purple as the evening wears on; and all this at the end of a long day in the operating theatre or consulting-room. For those who have to join the circus of presidents of the square dozen of metropolitan medical societies, dining out can become quite a habit between the autumn of one year and the spring of the next. And they all have to pay the same price for this hazardous privilege—making or listening to speeches. No one likes it—neither the speaker nor the listener. It is an intolerable infliction on all. There may be three or at the most four medical men in London, for example, who can make a speech that entertains. The rest conscientiously grind out their little stories or attempt displays of cleverness. Then comes the climax of after-dinner futility—the toast to the guests. The proposer, plainly, has met the most distinguished of them for the first time that evening; but he bravely hints at familiarity with their past, hoping he has not by error got hold of the wrong entry in *Who's Who*. On one memorable and even funny occasion the proposer brought a prompter with him in case he missed his cues. After-dinner speakers are mostly as dull as dish-water. It is not their fault. Surgeons have been taught to take life seriously, and physicians to look knowing and grave. Apart from their intrinsic demerits, after-dinner speeches prevent the diners moving round to meet old friends over the port. They all get stuck in their places next to and opposite the same old faces. If there must be speeches after dinner there should be two only—one for and one against, the choice of subject being open to the first speaker—and a time limit of seven minutes each.

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Drug Treatment of Disease

ASTHMA

BY

R. S. BRUCE PEARSON, D.M., F.R.C.P.
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The main advances in the symptomatic treatment of asthma lie in the use of corticoid substances and their derivatives. The older bronchodilators, however, remain the drugs of choice in cases of mild or moderate severity. Their effectiveness in some cases has been improved by modification in their structure, in their physical state, or by the combined use of more than one preparation, so that side-effects have been reduced or the rate of absorption modified. The use of the following preparations in asthma will be discussed :

(1) Bronchodilators: (*a*) Sympathomimetic drugs.
(*b*) Xanthine derivatives.
(*c*) Miscellaneous.
(2) Corticoid preparations and corticotrophin.
(3) Sedatives.

Sympathomimetic Drugs

These include adrenaline, isoprenaline, methoxyphenamine, and ephedrine. Ephedrine (30 mg.) and methoxyphenamine (100 mg.) are given by mouth and may be used in the treatment or prophylaxis of mild attacks. They are also useful in emphysematous patients with bronchospasm. Though they are less potent than isoprenaline or adrenaline, their action persists for a longer time. Isoprenaline can be prescribed sublingually in doses of 10–20 mg. or as an aerosol 1% hand spray. Inhalations of the aerosol delivered by means of pressure from an oxygen cylinder or electric motor may be continued for 15–30 minutes in exceptional circumstances. Adrenaline hydrochloride (1:1,000) 0.5–1.0 ml. or bitartrate (1:2,000) 1–2 ml. are given subcutaneously in severe attacks. Repeated doses of 0.05–0.1 ml. every 1–2 minutes may be given in status asthmaticus up to a total dose of 3.5–5 mg. of the adrenaline salt, unless there is relief of symptoms or evidence of hyperadrenalinism before the maximum dose is reached.

The side-effects of these drugs are mainly cardiovascular. Ephedrine, adrenaline, and isoprenaline are all cardiac stimulants and may cause extrasystoles or over-action of the myocardium, with unpleasant subjective sensations. Ephedrine is also a central stimulant and may make patients feel so tense and excitable that they are unwilling to continue taking it; for the same reason it may prevent sleep if administered at night. It is remarkable that this effect is rarely observed in children, who can usually tolerate ephedrine in doses of 8–15 mg. (⅛–¼ gr.) up to 5 years and 15–30 mg. (¼–½ gr.) after this age when it is given at bedtime, without any disturbances of sleep habit. Its prolonged action makes it a particularly valuable nocturnal prophylactic. The following linctus is often beneficial for children, and is suitable for a child aged 5 years:

℞	Tinct. camph. co. ..	minims 5 (0.3 ml.)
	Oxymel scillae ..	minims 15 (0.9 ml.)
	Ephedrin.	gr. ¼ (16 mg.)
	Pot. iodid.	gr. 1½ (100 mg.)
	Aqua chloroform ..	to 1 dr. (3.5 ml.)

One drachm to be taken before going to bed.

Methoxyphenamine ("orthoxine") is an analogue of ephedrine but produces considerably fewer cardiovascular or central nervous side-effects. When given to 7 patients who were unable to tolerate ephedrine, no side-effects were experienced in 6; and, of 24 patients who were asked to compare the effects of the two preparations, 15 preferred orthoxine (100 mg.) and 3 ephedrine (30 mg.). The bronchodilator effects of the two preparations were judged to be approximately equal.

The side-effects of ephedrine may be reduced by prescribing it with phenobarbitone 30 mg. (½ gr.) or sodium amytal 50 mg. (¾ gr.). Its action can be further prolonged by giving it in the form of a resin ephedrine complex, so that the ephedrine is liberated slowly by ion exchange as it passes down the alimentary tract. It has been shown that the active part of a combination of this type is in fact absorbed steadily into the blood stream over a period of 6–8 hours. The action of adrenaline can be prolonged by injecting a combination of adrenaline in an emulsion of nut oil ("hyperduric adrenaline"). Although these modifications of adrenaline and ephedrine may make them more effective under certain circumstances, the unmodified preparations are adequate for most patients and considerably cheaper.

Xanthine Derivatives

These consist of theophylline and caffeine. The former is the more effective and may be given orally, intravenously, or intramuscularly. Oral theophylline exerts a relatively weak bronchodilator action when given alone in the usual dose of 200 mg. (3 gr.). In severe asthma or in status asthmaticus, intravenous aminophylline (theophylline with ethylenediamine) 250–500 mg. should always be given if adrenaline has not been effective; it may cause dramatic relief in such patients. Rectal suppositories (250 mg.) are sometimes useful, especially at night. Side-effects are due to gastric irritation, especially when taken orally, and to cardiac stimulation (rarely with ventricular fibrillation) when injected intravenously. Administration by rectal suppository, though inelegant, seldom gives rise to unpleasant symptoms.

Various means have been adopted to avoid the irritating effects of theophylline on the gastric mucosa, of which the most obvious is to prescribe it after food. A combination with choline (choline theophyllinate) which increases its stability and is highly soluble appears to be the most effective; it is available in tablets of 100 and 200 mg. A preparation in which theophylline and aluminium hydroxide are given together is also well tolerated. The cardiac side-effects of intravenous aminophylline can easily be overcome by slow administration, and in status asthmaticus it may be given in a saline drip up to a total dose of 3 g. in 24 hours. The inconvenience of intravenous administration can be avoided by intramuscular injection, but this is painful because of the acid reaction of aminophylline. Modification of theophylline by replacing the hydrogen-containing amine with a hydroxy-propyl chain, diprophylline ("neutraphylline"), renders it neutral in reaction and relatively painless. The effect produced is somewhat slower than after intravenous administration. Caffeine is not administered alone for its bronchodilator action, but the *National Formulary* preparation, caffeine iodide elixir, is sometimes of value when bronchial infection is associated with asthma.

Although it is generally regarded as bad practice to prescribe more than one drug at a time, the effect of a combination of sympathomimetic and xanthine substances may be superior to that of either drug alone. The further addition of a sedative not only reduces the side-effects of ephedrine but may help to relieve nervous tension. Clearly, however, to be effective these drugs should be given in adequate quantities—that is, theophylline 130–200 mg.,

ephedrine 20–30 mg., and phenobarbitone 20–30 mg. The addition of a keratin coating will delay absorption of the active principles and makes such preparations particularly valuable in preventing nocturnal attacks.

Other Bronchodilators

The belladonna alkaloids and the nitrites, both pharmacological bronchodilators, are of no significant value in the treatment of asthma. Stramonium is sometimes given in the form of mist. pot. iod. and stramonium (*N.F.*) ½ fl. oz. (14 ml.) three times a day. Khellin, a smooth-muscle relaxant with irritant effects on the alimentary tract, has no advantage over better-known preparations. The antihistamines, though highly effective in many cases of hay-fever and urticaria, are disappointing in asthma. The sedative side-effects of promethazine and diphenhydramine, combined with their antihistaminic action, may render them effective in the nocturnal asthma of children, and in Great Britain their use in asthma is almost limited to this type of case. Diphenhydramine may be prescribed as an elixir as follows:

℞	Diphenhydramine	0.08 g.
	Chloroform	0.1 ml.
	Lemon flavouring ..	0.12 ml.
	Liq. ext. liquorice ..	0.3 ml.
	Soln. of bordeaux B ..	(*B.P.C.*, 1949) 0.08 ml.
	Soln. burnt sugar	(*B.P.C.*) 0.1 ml.
	Syrup	to 28.5 ml.

4 ml. to be taken at bedtime.

Corticoids

Corticoid preparations are highly effective in asthma. They are, however, merely symptomatic remedies and in no sense to be regarded as a "cure." While there is little objection to their use for short periods as a means of helping a patient through an exacerbation, their continuous exhibition, though justified in some cases, has certain serious disadvantages and should be avoided unless the patient's way of life is disorganized by his asthma.

Corticoids should be given only under the closest supervision and in exceptional circumstances if a patient has a history of peptic ulcer or pulmonary tuberculosis. Haematemesis from an ulcer, or perforation, with masked symptoms, are not uncommon even with short courses of treatment. The author is aware of three fatal cases and has seen others who survived. Reactivation of quiescent pulmonary tuberculosis may also occur. In diabetes, corticoids should be employed with circumspection and the dose of insulin may need adjustment. Signs of heart failure should also be regarded as a contraindication to the administration of cortisone and hydrocortisone; prednisolone or prednisone, which do not cause excessive retention of sodium and fluid, are relatively safe in this respect.

Intermittent Therapy

My own practice is to supply patients who are subject to intermittent severe attacks of asthma which may lead to status asthmaticus with an emergency supply of 20 tablets of prednisolone (5 mg.) or cortisone (25 mg.), and instructions to take these if their asthma fails to respond to the bronchodilator drugs they habitually use. The course of treatment is as follows:

Prednisolone 5 mg. or cortisone 25 mg.

Days 1 and 2	1 tablet four times a day.
Days 3 and 4	1 tablet twice a day.
Days 5 and 6	1 tablet twice a day.
Days 7 and 8	1 tablet at night.

This is effective in controlling exacerbations in a high proportion of cases, but patients with more severe attacks may need a larger initial dose—say, 7½ mg. four times a day for the first two days, thus prolonging the treatment to a period of ten days. Short courses of this type, even if repeated every month or so, are preferable to continuous or long-term treatment.

In status asthmaticus an initial daily dose of 60 mg. of prednisolone or 300 mg. of hydrocortisone should be given in divided doses on the first day. An initial administration of hydrocortisone hemisuccinate (100 mg.) intravenously is valuable in severe cases: this may be repeated after 3–4 hours if necessary. It must be remembered that immediate relief is not always obtained; corticoids do not act directly as bronchodilators, and improvement may not take place for 48 hours or more. Bronchodilator drugs such as adrenaline and aminophylline must therefore be given in the usual way until relief is evident. Death from asthma can still take place on full doses of corticoid substances. It is also important to remember that if bronchial infection is present antibiotics should be given in full doses.

Long-term Treatment

The long-term treatment of severely disabled asthmatics should be undertaken only after complete hospital investigation has been carried out with trial periods on corticoids and dummy tablets. It is important to bear in mind that patients who have been on even small doses of corticoids for more than a few weeks will have complete suppression of their suprarenal activity, and recovery of function will develop only slowly after the administration of corticoids has ceased. This means that under conditions of unusual physical or mental stress—for example, following surgery or during infection—such patients are unable to produce the additional secretion of corticoids which takes place under natural conditions when their output may be increased four or five times above the normal value. Inability to do this may lead to shock and sudden death, if additional corticoid substances are not provided on the day of and for some days after operation. Every patient on long-term corticoids will be well advised to carry a card stating the nature of the corticoid being used and the dose prescribed, with instructions to increase this by three or four times for 2–3 days in the event of emergency surgery, with gradual decrease to the usual maintenance dose over the next week.

.....Hospital

CORTICOID THERAPY

Name..... Hospital No.....

Address .....

.....

This patient is taking .....
regularly. It is important that the dose should not be decreased suddenly because the activity of her own suprarenal cortex is almost certainly depressed. In the event of any surgical emergency, the dose should be increased considerably for 48–96 hours after operation and then gradually reduced to the basic level.

Signed .....

Date.....

In the same way during respiratory infection the dose of cortisone may need to be increased and antibiotics should be used at the same time.

If these precautions are kept in mind cortisone or prednisolone in small doses can transform the life of a severely incapacitated patient. In a number of cases under my care, a dose of 5 or 10 mg. of prednisolone has enabled them to carry out their occupation with only occasional loss of time from asthma over a period of two years or more, whereas previously they had required repeated admission to hospital in status asthmaticus and were disabled between attacks. Other cases may require 100 mg. of cortisone or 20 mg. of prednisolone to obtain reasonable relief, but side-effects will be proportionately increased. In some cases the effect of the preparation appears to diminish after a few months. Prednisolone has the advantage that salt is retained only to a small extent, and the tendency to put on weight is much less than with cortisone.

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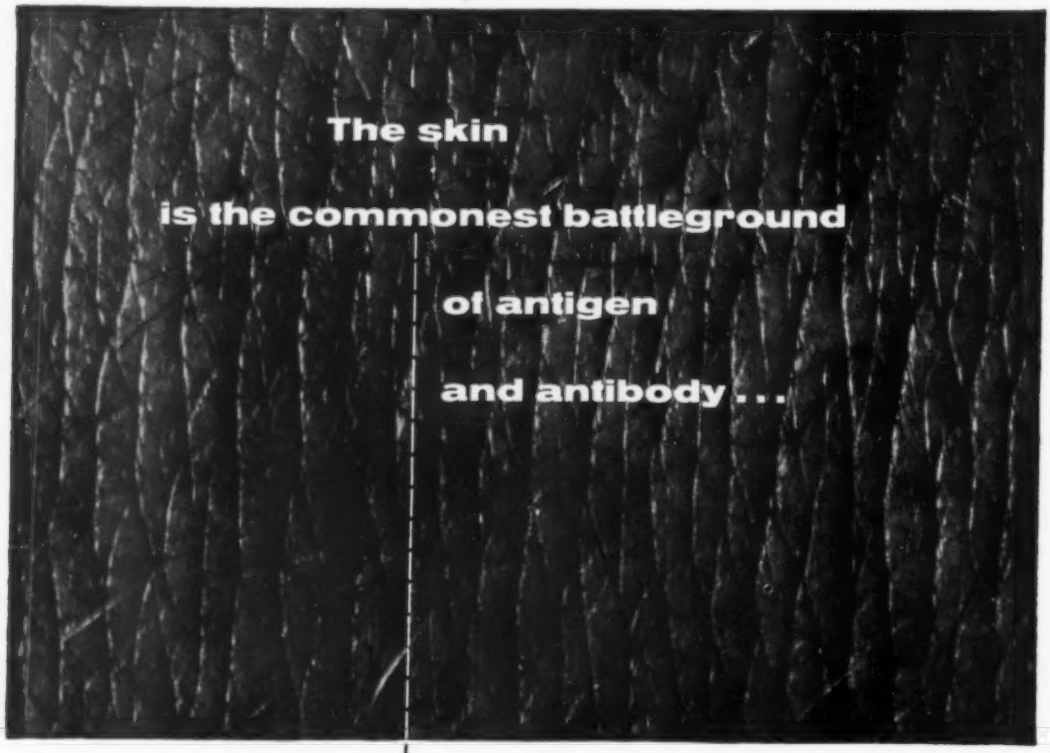

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When once corticoid treatment has been instituted for some months, the problem of weaning the patient becomes a difficult one. After such treatment it can be taken that the suprarenal cortex will cease to function. Heavy stimulation with corticotrophin in such cases will produce a temporary rise in corticosteroid output, but even this may lead to exhaustion of the cortex, with symptoms of acute Addison's disease. Abrupt termination of treatment will often lead to severe status asthmaticus, and all patients should be warned of this. Reduction of the maintenance dose when it has been given for six more months must be very gradual —say, 2½ mg. of prednisolone every 2–3 weeks. In many cases the patient must be prepared to continue on maintenance corticoid therapy for life. For this reason it is obviously a form of treatment rarely advisable for children, who will, however, tolerate short courses well.

Long-acting corticotrophin given intramuscularly is an alternative form of treatment which is not complicated by suprarenal suppression. It has the disadvantage that it must be given by injection and that obesity like that in Cushing's disease, with increase of several stones in weight, often develops. In rare cases sensitization to the animal proteins which are present as an impurity may occur, with production of anaphylactic shock. Death from anaphylaxis, however, usually follows only intravenous administration of corticotrophin. 20–40 units of corticotrophin may be given daily or on alternate days with benefit, and many cases have been kept relatively free from attacks in this way.

Sedatives

The well-recognized fact that emotional factors play an important part in asthma suggests that sedative drugs may be useful. There is some evidence that sodium amytal or phenobarbitone in small regular doses may help the nervous asthmatic, but their main value appears to be in combating side-effects of sympathomimetic agents. In status asthmaticus paraldehyde 5 ml. intramuscularly, or 2–4 dr. (7–14 ml.) by mouth remains the safest and most effective sedative for use at night. Morphine is contraindicated because of its depressing action on the respiratory centre. Pethidine, though a less effective sedative, is a mild bronchodilator with some depressing effect on respiration; its total effect is to reduce the tidal volume in the majority of cases. It is, however, reasonable to give it in association with nalorphine (4 mg.) when discomfort is great and other treatment has failed.

Conclusion

In conclusion it may be said that drug therapy, though valuable in asthma, should never be used as an excuse for avoiding the careful investigation of the important precipitating factors in each case, nor should the use of drugs replace measures to improve the general health. The recognition of allergic sensitization, emotional stress, or infection, and their treatment, are always of primary importance, and may lead to long-lasting relief that drugs cannot achieve. In particular the use of corticoids as the first choice of treatment cannot be deprecated too strongly.

The wise administration of bronchodilators is a useful accessory to other forms of treatment. They help to give the patient confidence in relieving symptoms, and may help to break an "asthma habit." Sometimes, because of our ignorance of the underlying pathogenesis, they may provide the only effective treatment available. In the same way corticoids may be used to prevent attacks of status asthmaticus or to control them when they have developed, and in a few cases may convert a disabled, unhappy patient into a relatively normal person capable of carrying out a full day's work.

It must be remembered that the objective in treating asthma to-day is to teach the patient to control and live with his disease. To do this intelligently he must be taken into the doctor's confidence and given some explanation of the rationale of the treatment recommended.

ORAL PENICILLIN IN GENERAL PRACTICE

BY

DAVID WHEATLEY, M.D.

Northern Home Counties Faculty, College of General Practitioners

Oral penicillin preparations have been in use for nine years, and yet the value of this method of giving the antibiotic is still the subject of considerable controversy. The reason for this may lie in the fact that oral penicillin therapy is almost exclusively administered by general practitioners rather than by hospital specialists. The former encounter innumerable obstacles in making public their observations, and hence there are few reports on the clinical use of oral penicillin. The paper by Chapple *et al.* (1956) is a notable exception to this.

On the other hand, from our hospitals have emanated a number of reports on the blood levels achieved with different oral penicillin preparations administered to healthy volunteers (Fairbrother and Daber, 1954; Laurance and Alder, 1954; Holborow *et al.*, 1956; Henry *et al.*, 1957; to mention but a few). The scarcity of reports on blood levels in ill patients is remarkable. In any case, blood levels are not necessarily related to therapeutic effect (*Brit. med. J.*, 1953). An article on the use of penicillin in sore throat included the statement that intramuscular penicillin rather than oral antibiotics was commonly used in practice for this complaint (Brumfitt and Slater, 1957). In subsequent correspondence I suggested that, on the contrary, oral penicillin was probably used far more in general practice than penicillin by injection (Wheatley, 1957). Through the co-operation of the research committee and members of the Northern Home Counties Faculty of the C.G.P., I have now had an opportunity to verify this statement and to collect further information on the subject from those most intimately concerned with it.

Objects of the Investigation

The objects were to find out how much general practitioners use oral penicillin, for what purposes they use it, and in what form and dosage. It is difficult to assess objectively the merits of this form of treatment, yet I feel that after this length of time general practitioners are unlikely to go on using oral preparations if in fact they are useless.

The faculty consists of some 180 members and associates distributed throughout the four counties—Middlesex, Hertfordshire, Bedfordshire, and Essex. Therefore all types of practice ranging from rural Essex to suburban Middlesex are included in the area, which constitutes a fairly representative cross-section of the country as a whole. These doctors were all circulated with a questionary asking the following questions:

1. Do you use oral penicillin? Yes/No.
2. Do you use it for Adults/Children/Both?
3. For which of the following infections do you use it therapeutically? Tonsillitis. Acute otitis media. Pneumonia. Acute bronchitis. Any others? (please state which).
4. Do you use oral penicillin combined with a sulphonamide, and if so, for what infections?
5. What preparation(s) do you use?
6. What is your dosage regime?

	(a) Dose	(b) Interval Between Doses	(c) Average Length of Treatment
Adult	..... units ..... or mg.	..... hours	..... days
Children 0–5	..... units ..... or mg.	..... hours	..... days

7. Do you consider that oral penicillin as given by you for the infections stated is: (*a*) Better than, (*b*) comparable to, (*c*) worse than penicillin by injection.
8. Will you kindly record over a 20-day period the number of cases for which you prescribe sustained penicillin treatment: (*a*) orally, (b) by injection.

N.B.—By "oral penicillin" is meant penicillin to be swallowed in the form of tablets, capsules, or mixtures. This does *not* include penicillin lozenges or other forms of local medication.

Participants were asked to return the forms, whether or not they were oral-penicillin enthusiasts.

Eighty-five (47%) doctors agreed to take part in the investigation and sent in completed questionaries, with the following results.

Use of Oral Penicillin

Eighty doctors (94%) replied that they used oral penicillin, against five who replied that they did not. Of the 80 doctors using it, 66 (82%) used it for both adults and children and 14 for children only. The number of patients treated orally and parenterally over a 20-day period were summated with the following totals: oral, 1,043 (73%); injections, 379 (27%). So that, for every two cases treated with penicillin by injection, five cases were treated orally.

The number of cases treated with penicillin over this period varied enormously from practice to practice. Thus one doctor treated the staggering total of 92 cases orally and 12 by injection, an average of five cases a day. At the other extreme one doctor treated only one case by injection during the period. Most replies, however, fell in the proportion shown by the total number of cases, with an average of 17 treated during the period. This amounts to almost one case a day, so it is apparent that a considerable amount of penicillin is used in general practice. It must also be pointed out that the survey was conducted during the month of May, which was a fairly slack period, and the figures would doubtless be higher for the winter months.

Infections Treated with Oral Penicillin

The four infections named in the questionary were correctly chosen as those for which oral penicillin was most often used, with furunculosis and boils coming very close to them. These and other conditions noted by the participants are shown below. The percentage of doctors treating each condition with oral penicillin is also shown:

Tonsillitis	91%
Acute otitis media	88%
Acute bronchitis	69%
Pneumonia	47%
Furunculosis and boils	44%
Finger infections	20%
Carbuncles, dental sepsis, acute sinusitis, scarlet fever, cellulitis (each)	6–10%
Upper respiratory infections, impetigo, phlebitis, mastitis, erysipelas, cervical adenitis, P.U.O., Vincent's angina (each)	3–5%
Urinary infections, bronchiectasis, acute pleurisy, acute conjunctivitis, acute laryngitis, vaginitis, Bartholinitis (each)	1%

Fifteen doctors volunteered the information that they used an initial "loading" dose of parenteral penicillin in the treatment of pneumonia or other infections if they were severe.

With regard to the use of oral penicillin combined with a sulphonamide, 17 (21%) doctors replied that they used this combination whereas 63 (79%) did not. Those using the combination did so for the following conditions:

Pneumonia	8 (47%)
If penicillin alone fails	5 (29%)
Acute bronchitis, acute otitis media (each)	5 (29%)
Boils and carbuncles	2 (11%)
Acute sinusitis, puerperal pyrexia, and chronic bronchitis (each)	1 (6%)

Choice of Preparation

Some doctors replied that they used more than one of the main varieties of oral penicillin, while some used one kind for children and another for adults. As a result the figures shown below do not represent percentages of the total numbers replying, but the proportionate figures for the different preparations:

	Children	Adults
Penicillin V (phenoxymethylpenicillin	52 (65%)	60 (75%)
Benzathine penicillin	29 (36%)	8 (10%)
Penicillin G (benzylpenicillin)	16 (20%)	11 (14%)
Penicillin+probenecid	5 (6%)	3 (4%)
Penicillin V + sulphonamide combination	2 (2%)	3 (4%)
Benzathine penicillin+sulphonamide combination	1 (1%)	1 (1%)
Penicillin G + sulphonamide combination	3 (4%)	3 (4%)

It is seen, therefore, that penicillin V is "sweeping the field," since more doctors used this than they did all the other preparations put together. Three-quarters of the participants used penicillin V for adults, although for children benzathine penicillin still remained fairly popular. This is doubtless due to the fact that penicillin V was first introduced in the form of tablets and capsules, whereas the palatability and stability of benzathine penicillin mixtures had been established before the introduction of the former.

There is no clinical evidence that penicillin V is any more effective than penicillin G in twice the dosage. Certainly the latter, even in twice the dosage, remains less expensive than penicillin V, although the price of this preparation may fall with continued usage. Nevertheless it is obvious from this investigation that penicillin V is almost completely ousting penicillin G for oral therapy. Undoubtedly this is due to the fact that penicillin V is more acceptable to the profession owing to reports of higher and more consistent blood levels after its administration. However, as has already been pointed out, these reports have been mainly on healthy volunteers. There remains a need for a therapeutic trial in ill patients.

With regard to penicillin and sulphonamide combined preparations, it is apparent from the previous section that this form of therapy is not particularly popular. Of those using it, 47% made use of the proprietary combinations available, although it might be thought that the dose of penicillin in these is somewhat on the low side.

Dosage Schedules

The only distinction which need be made between the different preparations is between penicillin V and the others. Since approximately twice as much penicillin V is absorbed as either benzathine penicillin or penicillin G, lower dosage schedules would we expected for the former. Therefore various dosage schedules were tabulated for penicillin V and the others, with the numbers of doctors using each scheme.

The most important results from these tables can be summarized thus: *For children:* 66% of doctors used penicillin V in a dosage of 60 mg. three to six hourly, while 65% used the other preparations in a dosage of 125–187 mg. three to six hourly, which is two to three times the dose of penicillin V. Only 5–6% used an eight-hourly scheme for either preparation. *For adults:* 61% of doctors used penicillin V in a dosage of 125 mg. three to six hourly, which is precisely double the most popular dosage scheme for children. Only 4% used an eight-hourly schedule for penicillin V, and the numbers for the other preparations were too small for analysis.

With regard to duration of treatment, the following results were obtained:

	Children	Adults
3 days	6	4
4–5 ,,	53 (78%)	47 (78%)
6–7 ,,	7	7
10 ,,	2	2

In other words, 78% of doctors favoured treatment for four to five days, without distinction between children and adults.

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Impressions of the Effectiveness of Oral Penicillin

The results were as follows:

Better than penicillin by injection	1	
Comparable to " " "	59	(75%)
Worse than " " "	20	(25%)

Of the 25% who considered oral penicillin to be less effective than penicillin by injection, one doctor stated that he was giving up using it orally. Of the others, several added their reasons for continuing to use it, the main one being dislike of giving injections to children. One doctor stated that he was allergic to injection solutions and so could not use them.

It is interesting to compare the dosage schedules used by those doctors who considered oral penicillin to be less effective than penicillin by injection. We can assume that an adequate dose of penicillin V is 60–125 mg. three to six hourly (the smaller dose corresponding to the shorter interval) for children, with double these doses for adults. For other penicillin preparations the doses are double those for penicillin V. We can also assume that at least four to five days' treatment is required for the simpler infections. By these criteria, eight out of these 20 doctors (40%) were using inadequate dosage, which might account for inferior results.

It is also instructive to see whether these 20 doctors were "practising what they preached," by noting whether they treated more cases by injection than by mouth. The results are illuminating: more by injection than orally, 6; more orally than by injection, 8; question not completed, 6. Of those treating more cases orally, the proportion of oral to injection recorded by three of them was very high—namely, 29:2, 92:12, and 7:0. The reason for this apparent anomaly is probably summed up in the words of one of these doctors: "Oral penicillin is only slightly less effective than intramuscular penicillin, a disadvantage greatly outweighed by its greater convenience, particularly with children."

Conclusions and Summary

The Northern Home Counties Faculty of the C.G.P. has some 180 members distributed in all types of practice. Of these, 85 (47%) agreed to answer a questionary on the use of oral penicillin in general practice.

It was found that oral penicillin was used by 92% of these doctors, of whom 82% used it for both children and adults and the remainder for children alone. The total proportion of cases treated orally to those by injection over a 20-day period in May was 5 to 2. It would seem likely that these results, coming from such varied practices as they do, are representative of national custom. This being so, it may well be that more penicillin is now given by mouth in this country than by injection.

Of the infections commonly treated with oral penicillin, tonsillitis (91%) and acute otitis media (88%) came first, with acute bronchitis (69%), pneumonia 47%), and minor boils (44%) next. Finger infections accounted for 20% and a large number of other miscellaneous conditions fell into the 1–10% range. These results reflect the common penicillin-sensitive infections met with in general practice, with the exception of severe deep-seated infections, such as carbuncles, which are probably best treated with penicillin by injection.

With regard to the preparations used, it is apparent that penicillin V (75% for adults, 65% for children) is "sweeping the field," although benzathine penicillin in its palatable liquid form still retains a place in the treatment of children (36%). Combined penicillin and sulphonamide therapy would not appear to be particularly popular, only 21% of the participants using it. The indications were for serious infections such as pneumonia or other infections which had failed to respond to penicillin alone.

Dosage schedules used by the participants showed very wide variations. However, 66% of doctors used penicillin V in a dosage of 60 mg. three- to six-hourly for children of 0–5 years and 61% used double this dose for adults. The dose used for other preparations was two to three times the above for adults, the numbers being too small to analyse for children. This would seem to reflect fairly accurately the difference between the amount of penicillin V absorbed from the gastrointestinal tract and that absorbed from other penicillin salts. 78% of the participants favoured four to five days' treatment for the infections listed.

One doctor thought that oral penicillin was better than penicillin by injection; 75% of the participants found the two forms comparable. Of the 25% finding oral medication not as good as injection, 10% were probably using inadequate dosage. More of these doctors continued to use oral rather than injected penicillin, despite their impressions of the relative efficiency of the two methods. This is probably because they found oral penicillin to be effective enough to allow its advantages to overcome any slightly diminished therapeutic effect. However, it is apparent that the majority of general practitioners taking part in this survey were completely satisfied with the effectiveness of oral penicillin therapy.

This investigation could not have been undertaken without the co-operation of the following doctors who took part in it: G. S. Adams, M. S. Adams, E. Anthony, C. D. Baker, D. M. Baker, G. O. Barber, L. J. Blay, W. N. Booth, O. B. Brears, H. M. Brunt, R. B. Chalmers, D. S. Chowdhary, J. R. C. Clarke, M. B. Clyne, G. H. R. Curnock, J. A. Currie, D. Craddock, L. R. Dennis, H. B. Dykes, G. W. Everett, R. A. Fisher, E. D. Fox, R. P. Gammie, J. Z. Garson, J. C. Graves, J. D. Granger, D. Gregory, R. A. Haes, A. A. Hamza, B. H. du Heaume, J. E. Heggart, R. N. Herson, E. R. Herst, S. F. Hewetson, F. N. Hicks, H. Jarvis, J. D. S. Knight, M. Latner, R. Lawson, A. J. Levine, I. M. Librach C. R. Lynn, G. McDonnell, J. H. Macpherson, G. Melotte, P. J. Mitchell, K. E. Mortimer, T. M. Moylett, P. D. Mulkern, H. M. Murray, B. E. H. Neal, J. O. Newman, N. G. Nicholson, N. O. Patterson, N. L. Paros, J. T. Pembleton, A. G. Philip, P. B. Poole, S. M. Pruss, B. S. Quinn, W. Radcliffe, D. A. G. Reid, C. J. P. Seccombe, I. M. Segal, F. S. Shepherd, F. S. W. Shute, S. G. A. Shute, B. C. Slater, R. N. C. Smith, W. J. Smither, G. E. Spear, J. D. Swan, V. W. Symonds, J. L. Tasker, M. E. Thorn, J. Totton, J. C. Turner, P. de B. Turtle, P. A. Walford, M. A. Weller, D. Wheatley, G. B. Whitaker, M. Williams, D. G. Wilson, G. C. L. Woodroffe.

ADDENDUM.—Since the above was compiled, two articles have appeared on the clinical use of penicillin V, in chest infections (R. Lamb and E. S. Maclean, *Brit. med. J.*, 1957, 2, 191), and in pyogenic lesions (J. I. Burn, M. P. Curwen, R. G. Huntsman, and R. A. Shooter, *Brit. med. J.*, 1957, 2, 193). These reports confirm the effectiveness of penicillin V by mouth.

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The Excerpta Medica Foundation, Amsterdam, announces the publication of a new monthly abstracting journal, devoted to rehabilitation. This forms Section XIX of the *Excerpta Medica* series. Its cost of production is aided by a grant from the Department of Health, Education, and Welfare of the U.S. Public Health Service. Annual subscription is $15.

SOCIETY FOR SOCIAL MEDICINE

SECOND ANNUAL MEETING

[From a Special Correspondent]

The Society for Social Medicine held its second annual meeting at the Moyne Institute, Trinity College, Dublin, on September 26 and 27, under the chairmanship of Professor W. J. E. Jessop. Following the precedent established the previous year in Birmingham, the programme during the first morning was chiefly left to the hosts.

Teaching of Social and Preventive Medicine

First, Professor Thomas Murphy (University College, Dublin) and Professor W. J. E. Jessop (Trinity College, Dublin) outlined the principles upon which their teaching programmes are based, and Dr. R. M. Acheson (Trinity College, Dublin) described a series of courses in preventive medicine he was running at the patient's bedside. The object behind these was to encourage the student to think about the factors which cause a person to attend his doctor, and what, in addition to the more urgent questions of diagnosis and treatment, the practitioner can do to prevent recurrence of illness. In the ensuing discussion Dr. S. W. Hinds (London School of Hygiene and Tropical Medicine), who has had 10 years' experience of such teaching, said that he found it to be far more effective at the bedside of a child than at that of an adult. Dr. John Phair (University of Cincinnati), however, thought that a living patient was unnecessary, and in his opinion the most effective way of putting across preventive and social medicine was for small groups of students to consider a written case history or situation.

After the coffee break, members of the Trinity College department presented a short symposium on the longitudinal anthropometric research they have been carrying out. Mr. E. H. Thornton had analysed data which consisted of two measurements of the standing height of a group of employees of Messrs. Arthur Guinness, Son, and Co., with many years intervening between them, and concluded that between the ages of 25 and 75 the average man could expect to shrink by about three-quarters of an inch (19 mm.). The growth of some 100 girls living in a residential institution, whose stature had been measured regularly every three months for the greater part of their childhood, was the subject of papers by Dr. Mavis Archer and Dr. Acheson. They had found that a physical illness such as an exanthem, or the psychological disturbance of admission to the institution, both slowed growth significantly. There was some suggestion that a compensatory growth spurt followed, but it was too early to assess its importance.

Social Grading and Observer Variability

Several papers dealt with two very important methodological aspects of group research. Dr. J. W. B. Douglas (Edinburgh) described the considerable changes in social background and classification experienced by many of the families he had followed in the course of the National Child Health Survey. In elaborating the difficulties these presented to the research worker he gave the instance of a family in which the father had been an artisan throughout the 13 years of the Survey, yet had been able to buy a house, equip it fully with modern labour-saving devices, and send his family of three children to fee-paying schools. Dr. F. M. Martin (Edinburgh) also dealt with the problem the research worker faces when he attempts an adequate classification of social status. The Registrar-General's system of five classes graded according to the occupation of the husband was a convenient shorthand, and was probably fairly efficient for Classes I and II, but tended to fall down badly in the case of manual workers. In the ensuing discussion it was pointed out that there is no method at the moment for classifying the occupations of women, and the meeting seemed to be in agreement with Dr. Donal MacCarthy (Dublin) when he said that it seemed impossible to classify social status efficiently on any single criterion.

A paper by Dr. A. S. Fairbairn (London School of Hygiene and Tropical Medicine) describing the difficulty presented in grading respiratory symptoms objectively was read by one of his colleagues. The problem had been studied by tape-recording interviews in which four doctors and four social workers, each working separately, asked a group of subjects a series of questions from a printed questionary. Despite efforts at standardization, differences in the actual reading of the question and interpretation of the reply led to wide variation in assessment of symptoms. Other aspects of observer variation were described by Dr. I. T. T. Higgins and Dr. W. Miall (M.R.C. Pneumoconiosis Research Unit, Penarth), whose paper was concerned with the difficulties they had met with in using randomly selected controls in a prevalence study of diabetes and goitre in the valleys of South Wales.

Congenital Abnormalities

A session on developmental abnormalities was opened by Dr. I. Leck and Dr. R. G. Record (Birmingham), who pointed out that, although the stillbirth rate has been falling steadily, there has been no reduction in the incidence of congenital malformations. Major malformations were commoner among multiple births, and also in families whose income was low; on the other hand, less abnormal babies than expected were born to Rh-negative mothers. If a mother worked during her pregnancy, it would seem that her chances of bearing a mongol were slightly increased.

Dr. Victoria Coffey (Trinity College, Dublin) gave a preliminary report on a prospective study she had made on Dublin women who had been pregnant during the recent pandemic of Asian influenza, and who, when questioned during the antenatal period, said that they had had "'flu." There were over 600 mothers in this group, and the overall incidence of malformed babies born to them was 3.8% as compared with an incidence of 1.7% in a control group. Amongst the 88 women who had been ill during the first trimester, however, the incidence of congenital abnormalities was 9%. During the discussion Dr. Richard Doll (London School of Hygiene and Tropical Medicine) said that he had carried out a similar study of some 200 mothers whose diagnosis of "'flu" had been confirmed by a general practitioner; the incidence of congenital abnormalities among this group was about 3%, but there was no association between the trimester of pregnancy during which the mother was infected and the incidence of malformed babies. Dr. J. C. McDonald (Epidemiological Research Laboratory, Colindale) pointed out that as many as 40% of the mothers who had no symptoms of influenza were probably infected by the virus.

The third paper in this session was read in their absence for Dr. C. R. Lowe and Professor Thomas McKeown (Birmingham), and described a retrospective study of the effect of mothers smoking during late pregnancy on the birth weight of their babies; it seemed that, the more the mother smoked, the lighter her baby was likely to be. Dr. Josefine Webb (Oxford) pointed out that a great many women lose the taste for cigarettes early in pregnancy, and that this might to some extent bias the results. However, Dr. S. W. Hinds (London School of Hygiene and Tropical Medicine) said that his experience supported the conclusions of the Birmingham workers.

Use of Medical Services

Dr. R. F. Logan (Manchester) presented a detailed analysis which he and Dr. G. Forsyth had carried out of the use made of the State hospitals services in the Barrow area. Amongst other things, they found that, although morbidity at most ages was higher among males than among females, the admission rate of females to medical wards was higher than that of males. They attributed this to the inability of the average British husband to cope with a sick wife at home. Dr. Richard Scott and Miss Ann Cartwright (Edinburgh) then described the card system they have developed to analyse the work of the general practitioner training unit in Edinburgh University.

Dr. Lilli Stein (Maudsley Hospital, London) had analysed the attendance rates over some years of patients suffering from neuroses and psychosomatic complaints in a group practice in a stabilized area in S.E. London. The frequency of such complaints had been as high as was found by Brotherston and Martin* in a newly settled housing estate, and she suggested, therefore, that change of domicile might not be so important an aetiological factor in minor mental illness as the Edinburgh workers had suggested. Speakers from the floor pointed out the tendency for self-selection of patients to a practice because of the known interests of the doctor, but Dr. Stein replied that this danger was reduced in group practices where the partners' interests differed and the patient could not be sure which doctor he would see at a given consultation. Dr. F. N. Garratt and Dr. Lowe (Birmingham) showed that, compared with men, an increasing proportion of women aged 25–60 years are being admitted to mental hospitals in England. A local survey in Birmingham supported this finding and suggested that the female preponderance came from the more prosperous wards of the city. In reply to a question from Dr. Horace Joules (Central Middlesex Hospital, London), Dr. Garratt said that there was a higher incidence of mental illness among women living alone in the younger age groups, but that this trend was not so striking after middle age.

Aetiology of Acute Appendicitis

Dr. J. A. H. Lee (M.R.C. Social Medicine Research Unit, London) said that peak hospital admissions for acute appendicitis in boys occurred in early childhood and again at the age of 10–12 years; in girls, if allowance were made for the fact that pain attributed to appendicitis was often of gynaecological origin, there was probably also a peak of admissions for appendicitis at about the same ages. Death rates in boys from acute appendicitis were highest in the early teens. If it was accepted that appendicitis in early childhood was usually a misdiagnosed non-specific mesenteric adenitis, then the peak morbidity and mortality for boys, and morbidity for girls, occurred at about the time of puberty. Scammon had shown that this was the time of maximum development of lymphoid tissue, and such tissue subsequently regressed. Therefore, Dr. Lee suggested, the excess of lymphoid tissue in the appendix was a primary factor in causing obstruction of the lumen with subsequent stasis and inflammation, particularly in the male, where the muscular coat was probably thicker. Professor John Pemberton (Queen's University, Belfast) was not entirely satisfied with Dr. Lee's arguments as applied to girls, and Dr. Logan (Manchester) pointed out that tonsils and adenoids, which were also lymphoid tissue, had a very different age-morbidity pattern. He suggested that the adolescent boys' unwillingness to "go sick" was probably a major factor in their high mortality rate from appendicitis.

Dr. E. G. Knox (Birmingham) had been counting the aunts and uncles of propositi with hereditary diseases, and had found that a group of cases of limb-girdle muscular dystrophy had twice as many maternal aunts as were expected. In contrast, patients with Klinefelter's syndrome had a disproportionate number of paternal uncles; yet for groups of normal infants and of mongols the distribution of aunts and uncles appeared to be symmetrical. Replying to a question from Dr. Alwyn Smith (University of Malaya), Dr. Knox said that, although the data were not all his own, he had tried to allow for the fact that the mother of a propositus would give a more accurate account of her own siblings than of her husband's. The scientific business of the Society was concluded with a description by Mr. J. A. Heady (M.R.C. Social Medicine Research Unit) of a dietary survey he had been conducting among bank employees in Brighton.

The annual dinner was held at Trinity College, where Lord and Lady Moyne were the chief guests.

*See *Brit. med. J.*, 1957, **2**, 819.

MEDICAL PROTECTION SOCIETY

The 66th annual meeting of the Medical Protection Society was held at the Society's offices, Victory House, Leicester Square, London, W.C.2, on October 1. During 1957 the number of new cases considered by the Society was 2,054. The membership at the end of the year was 33,437, a rise of 3,146.

In his presidential address, Sir Ernest Rock Carling said the Society had extended its work very considerably throughout the Commonwealth, and a year's experience of this overseas work had shown it to be on the whole quite satisfactory. With the depreciation of money there had been an undoubted tendency for larger amounts to be awarded in damages and compensation, he continued, and therefore at some time they might be compelled to consider raising subscriptions. But in view of the Society's strong financial position that was unnecessary at the present time. (The ordinary subscription is £2.) Discussing some of the hazards of practice, Sir Ernest said that, when a patient changed from being an N.H.S. to a private patient, it was of the greatest importance that the change should be recorded in writing, and that the records of treatment under the National Health Service and privately should be kept separately and with extreme accuracy. The matter of accurate records was of the greatest importance. Sir Ernest commended the Berman's metal-locator, described by Professor Lambert Rogers, a member of the Society's council, which enabled the exact position of a metallic foreign body to be detected; every casualty department ought to have one. The treasurer, Mr. W. M. Mollison, presented the financial report. Income at £82,455 showed a rise of £16,516. Expenditure had risen by £18,097 to £86,927. The total funds available for the protection of members were now over £225,000.

X-rays and A.I.D.

Mr. W. G. Hawkins, solicitor, recalling that it was 10 years since the introduction of the National Health Service, said there was no doubt that the Service had produced a tremendous amount of work for the Society, not only because "what we believe to be the different relationship brought about by the National Health Service" had brought more litigation against doctors, but the Service itself had caused doctors and dentists to seek advice on countless problems arising out of it—problems of superannuation, terms of service, etc. Mentioning that cases of failure to diagnose mainly related to dislocations or fractures or tuberculosis, the solicitor said that there was usually a specific allegation that either the doctor had not taken a radiograph or he did not take one soon enough.

Professor Lambert Rogers said that, as a teacher of surgery, he advised *x*-rays, but also restriction in their use. A balanced judgment was needed. They should not take radiographs indiscriminately to guard against legal possibilities. In reply, Sir Ernest Rock Carling pointed out the attention now being given to the use of limited-field *x*-rays. "It is possible to get even better *x*-rays than we have had in the past with a smaller field and a smaller dose, and as that happens we shall be able to resume the use of *x*-rays to the full. It is well in hand," he said.

The solicitor, in his report printed in the annual report, states: "Although artificial insemination must by its very nature provide a source of legal complications affecting questions of legitimacy, inheritance, nullity, and divorce, it should not involve a doctor in any difficulty so long as he acts with care and discretion. The practitioner asked to carry out artificial insemination will be faced with no particular legal problem if the donor is to be the husband (A.I.H.). If the donor is to be someone other than the husband (A.I.D.), the position should be fully explained to the husband and the wife, and a request and consent in writing signed by both should be obtained." The solicitor's report also discusses the question of sterilization at the patient's request, stating that the doctor should satisfy him-

self that a definite danger to life or health exists, and should whenever possible have his opinion corroborated by at least one other practitioner. The effect of the operation must be fully explained to the patient, whose written consent should be obtained; if the patient is married, it would also be wise to explain the position to the spouse with a view to obtaining his or her consent.

However trivial or unjustified a practitioner may consider a complaint to an executive council, he is strongly advised, in the Society's report, to attend the Medical Service Committee hearing. "We know of instances when the practitioner has failed to attend, with the result that the evidence of the complainant, in the absence of the practitioner's rebutting evidence or explanation, has been accepted by the Committee."

NEW ACADEMIC YEAR

WELSH NATIONAL SCHOOL OF MEDICINE

The inaugural address for the new academic year at the Welsh National School of Medicine was given by Professor G. I. STRACHAN, emeritus professor of obstetrics in the School, at Cardiff on October 8. He reviewed some aspects of past professional life, and traced the factors—partly in the nature of the doctor's work and partly due to increasing Government control—that have led to its modification.

The Profession of Medicine

In the early nineteen-hundreds ours was a free profession, said Professor Strachan. The patient chose his own doctor and changed him when he thought fit, while an account for professional services was rendered from time to time. A doctor assumed a partner or an assistant at will, and on retirement or death the goodwill of his practice was sold to an appropriate successor. The doctor–patient relationship of mutual regard and trust was then an important feature of British medicine.

In 1911 the National Health Insurance Act was introduced. This required the wage earner and also his employer to contribute a weekly sum, and for this the former was entitled to receive appropriate medical treatment from the doctor of his choice. The Act was opposed by the British Medical Association, as it implied Government interference between patient and doctor. But only the wage earner was provided for; his family was not included under the benefits, neither were specialist or maternity services. For these reasons Government interference was not marked and a substantial degree of private practice persisted.

But in 1943 at the request of the Government Sir William Beveridge presented his report on national insurance as an integral part of the Welfare State. This established a comprehensive national health service which embraced everyone, rich and poor, and which provided for every kind of investigation and treatment—general, consultative, or hospital—together with all necessary drugs and appliances. These provisions were embodied in a Bill which became an Act of Parliament on July 4, 1948, the appointed day. The National Health Service represented a great upheaval in medical life and practice. The new Service was contributory, and, as it was taken advantage of by about 96% of the population, the Government now stood in a commanding position between doctor and patient. The doctor had now to look to the Government for all or almost all of his remuneration; he could not practise under the Service or take a partner or assistant without Government permission, while on death or retirement his successor was appointed by a committee. The Government took over all the public hospitals and became responsible for their maintenance. The honorary status of consultants ceased, and they were now remunerated on a sessional basis and at an annual salary. Rich and poor now sought hospital treatment, so that out-patient attendances rose sharply while waiting-lists became correspondingly congested. In general practice the "free" aspect of the Service stimulated patients literally to storm the surgeries of their doctors, often for the most trifling of complaints.

One result of the National Health Service had been a degree of deterioration in the doctor–patient relationship as shown by unreasonable demands on the doctor's services and for particular remedies, by a tendency to lodge complaints against the doctor before the executive council, and by a grave increase in litigation. The effect of this had been to cause reference to hospital of minor cases, often unnecessarily, while hospital officers now tended to carry out their work under conditions of uncertainty and apprehension. Again, prescribing was to some extent supervised, and, while great latitude was allowed in this respect, undue prescribing of the more expensive drugs might result in a heavy fine if it was considered that a less expensive drug would have been equally effective.

Medical life had altered materially in the last half-century. The doctor's responsibilities had increased while his status had to some extent decreased; he was more open to criticism, and his choice of place to practise in might be restricted. On the other hand he had better facilities for diagnosis and treatment and he was still held in regard. The material rewards in medicine had never been great, and the main reward must always be in work well done. In spite of altered conditions a medical man could still lead a full and happy life.

CHARING CROSS HOSPITAL

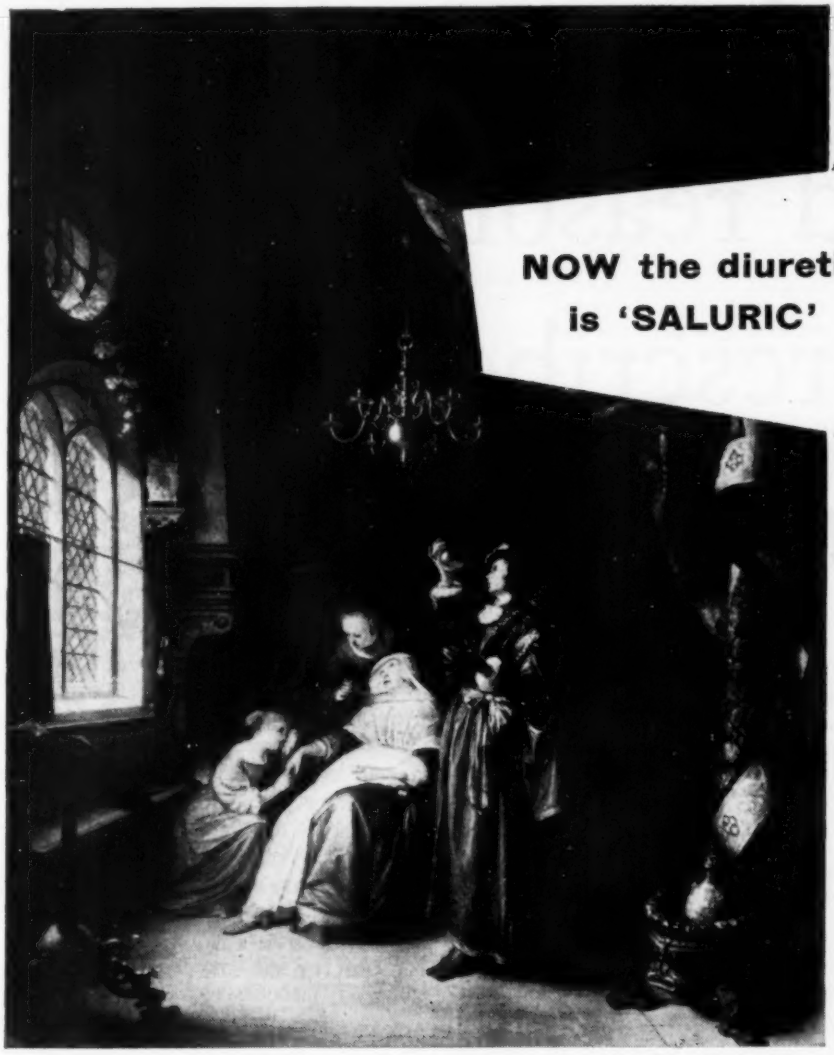
The importance of maintaining private practice was stressed by Sir HARTLEY SHAWCROSS, Q.C., when he gave the inaugural address at the opening-day ceremony of Charing Cross Hospital Medical School on October 2.

Value of Private Practice

Sir HARTLEY said he had been impressed by the great changes which had taken place in the position of the medical practitioner in the last thirty years. His prospects to-day were much more encouraging. "It is sometimes said that the National Health Service is a danger to the integrity and independence of doctors," he said, "and of course there are doctrinaire people who would like to abolish private practice and to do away with pay beds, just as they would like to abolish the public schools in an effort to reduce us all to a rather dull and drab equality. These are dangers which will be guarded against. I believe that the possibility of private practice and the existence of the independent schools is something which it is vital to maintain against the encroaching power of the almighty State. It is most important that the medical profession and the teachers should not become the slaves of a bureaucracy or the pawns of politics."

In the last thirty years the concept of social service had become so widely recognized that the medical practitioner could to-day call on the assistance of many ancillary services. The medical profession was the most satisfying of all, offering the greatest prize of all. Indeed, Sir Hartley had himself contemplated a medical career in his youth and had visited one of the London teaching hospitals with this in mind before turning to the law. Referring to the decision to rebuild the hospital in Fulham, Sir Hartley recalled that when Charing Cross Hospital was established 100 years ago it had dealt with the sick poor in a very crowded area. Since then there had been a great move of population. Fulham was now the centre of a thickly populated area, but it was near enough to the centre of London and the University to offer the facilities of the other scientific studies at London University.

In his annual report the dean of the medical school, Professor W. J. HAMILTON, said that in August last year the board of governors had been asked by the Ministry of Health whether they would be prepared to build the new Charing Cross Hospital and Medical School on the site of the present Fulham Hospital, incorporating in the new hospital Fulham Maternity Hospital, the West London Hospital, and the present Charing Cross Hospital. They had



"La Femme Hydropique" (The Dropsical Woman) by Gerard Dou, painted in 1665. The original hangs in The Louvre.
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agreed, and in July the Minister of Health had given final approval. "The board are convinced," he said, "that with the good will and co-operation of all concerned, the new hospital and medical school will constitute a landmark not only of local pride but also of national and indeed international significance. Assurances have been given to the Ministry that an adequate hospital service can be provided for the Fulham area and that the staffs of the Fulham Hospital, Fulham Maternity Hospital, and West London Hospital will be welcomed to the new Charing Cross staff without the slightest detriment to their existing contracts and conditions of service." It was the intention of the board of governors that, when the building of the new hospital was completed, the residents of Fulham would have a fully comprehensive medical service backed by all the resources of a modern teaching hospital. The general practitioners of the Fulham district would have the opportunity of becoming closely associated with the hospital by taking advantage of the facilities available to them for *x*-ray and pathological examinations.

The prizes were then presented by Lady Shawcross, and the appointment of Dr. N. F. Morris as professor of obstetrics and gynaecology was announced.

ROYAL FREE HOSPITAL

At the Royal Free Hospital School of Medicine prize-giving, held at the Senate House of London University on October 3, the inaugural address for the new session was delivered by Professor Dorothy Russell. Her subject was "Belief and Unbelief." After presenting the prizes and congratulating the winners, Professor Russell emphasized that those who had not distinguished themselves academically knew perfectly well that in future life many non-prize-winners made extraordinarily successful doctors. This was where the important factor of personality came in. There were many who knew of the brilliant scholar who tragically failed to gain some coveted post which would seem well within his grasp, because for some reason he was felt to be uncongenial to the small, closed society which formed a hospital staff. Hence, in the medical profession particularly, academic prowess was not enough. It was necessary also to learn to be a good colleague and to be recognized as such.

A Spirit of Scientific Inquiry

She hoped that, in the student's training, account had been taken of the concept of integration, which implied a synoptic view of the preclinical and clinical years. This was easy to state in so many words, but peculiarly difficult when it came to teaching; and in most medical schools only a beginning had been made to the dovetailing of clinical and preclinical studies so as to do away with the usually abrupt transition from one to the other. Self-education was another most important ingredient in the clinical term of undergraduate experience. It should take the student whenever possible to the post-mortem room. However distasteful it might be to witness this form of demonstration on a subject who had been seen in the wards, it was the sole means of reaching the truth, or, at least, the closest approximation to the truth. This form of diagnosis stamped itself upon the student's memory and he had it as part of his background of experience for all time.

Professor Russell advised students who would take their share in the advance of medical science to be ready to challenge the printed word if it did not agree with their own observations. They should be most reluctant to accept dogmatic teaching, however attractive it might seem. This was an era in which the art of medicine was constantly being encroached upon by the advance of scientific knowledge into the wards. They should, above all, observe objectively in every way possible what they found in their patients and maintain a cautious attitude towards all unsubstantiated statements, however plausible; and they should be humble enough to admit uncertainty when every justifiable investi-

(Continued at foot of next column)

To-day's Drugs

In this column we publish from time to time authoritative notes on a selection of drugs in current use.

Delta-Stab Injection (Boots Pure Drug Co. Ltd.).—This preparation consists of prednisolone acetate 25 mg. per ml., put up in a sterile aqueous suspension for intra-articular injection. It is used for its anti-inflammatory effect in various forms of arthritis, particularly rheumatoid. Its efficacy compared with hydrocortisone acetate, given as an intra-articular injection, is difficult to evaluate. Milligram for milligram it is certainly no less effective, but it has not the 4 or 5 to 1 superiority seen with the oral preparations of prednisolone, and dosage by the intra-articular route is therefore much the same as with hydrocortisone acetate. Before injecting these hormones it is essential to be certain that secondary bacterial infection has not been superimposed on an inflamed rheumatoid joint.

N.H.S. basic price: 5 ml., 30s.

Epidexa (Thomas Kerfoot and Co. Ltd.).—This is a mixture of a chlorocresol with a quaternary ammonium salt intended for use as an antimycotic and bactericide. It is available as a liquid, a cream, or a powder. Although reports of clinical trials of this particular preparation do not seem to have appeared, one may well expect that it will possess antiseptic properties *in vitro* and presumably in clinical use. It is intended by the makers chiefly for fungus infections of the skin but also for bacterial infection.

In recent years many antiseptic preparations have been put forward for the treatment of ringworm infections of the skin. Their number and variety are some indication of their relative inefficiency in spite of their being most efficient when tested *in vitro*. This seems to indicate that fungicide preparations fail not because they do not kill the fungus but because they fail to penetrate, or because they are in some way inactivated on or in the skin. For this reason many dermatologists have little faith remaining in the production and trial of fresh fungicides, and it often seems that Whitfield's ointment has yet to be surpassed.

With these reservations one may comment that epidexa is well formulated. Dichlorocresol is known to have a definite, though not excessive, potentiality of sensitizing the skin, and for this reason should be used circumspectly. It might thus be unwise to apply to the apparently normal skin for a long period as prophylaxis against athlete's foot, since the risk of sensitization increases with long duration of contact.

N.H.S. basic price: liquid, 2 oz., 7s. 7d.; cream, 25 g., 8s. 6d.; powder, 25 g., 5s. 5d.

(Continued from preceding column)

gation had proved fruitless. It was worth devoting as much thought as possible to novel methods of tackling clinical problems. Medical students had been known to make interesting and substantial additions to medical knowledge by this very technique of devising new methods of interpreting abnormalities seen in their patients.

The dean, Dr. Katharine Lloyd-Williams, described the school's continuous growth since its foundation in a private house in Hunter Street in 1874. It was now one of the four largest medical schools in London. In its 84 years of history it had been the first to do many things, and it might well be the first of the teaching hospitals to go in for a completely new modern hospital designed and equipped for medicine to-day. This had been a "pipe dream" for some years, but on the new 15-acre site at Lawn Road, Hampstead, there was the chance to plan a new teaching hospital and school, the first of its kind in the country to be designed specifically for the purpose. There was the same determination to make a success of this as had been shown many years ago by the founders, and the future could be looked forward to with confidence.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

R.M.B.F. Christmas Gifts Appeal

Sir,—Every autumn an appeal is made to members of the medical profession for contributions to the Christmas Gifts Fund organized by the Royal Medical Benevolent Fund.

To receive a gift at Christmastime is a joy to everyone, but particularly to those who are lonely or in need. To none is a gift more welcome than to those who have fallen on hard times. Our beneficiaries include colleagues who have met with misfortune, and widows and children who are often in desperate need when their breadwinner has been taken before he was able to make provision for them. A gift at Christmas will enable them to enjoy some of the traditional good cheer of the season.

I ask your readers once again to give generously. Contributions marked "Christmas Gifts" should be sent to the Secretary, Royal Medical Benevolent Fund, 1, Balliol House, Manor Fields, Putney, London, S.W.15.—I am, etc.,

Henry Tidy,
President,
Royal Medical Benevolent Fund.

Premonition of Death

Sir,—The mystery of premonition of death, of which Dr. Arnold B. Cowan gives such a good example (*Journal*, September 27, p. 797), has interested me since I first came across it in 1949. At the time I was working in a large Arab refugee camp in Jordan. Amongst my many patients was a youth of 16, whom I knew well, who was suffering from pulmonary tuberculosis. We were able to confirm radiologically that the condition was not far advanced and clinically his condition did not give cause for undue anxiety, though facilities for treatment were unfortunately very limited. There were two noteworthy features about this boy—firstly, he was simple-minded and was regarded in fact as something of a joke by his friends and relations; secondly, he was a very devout Moslem. His father, a sheikh, had formerly been a man of some wealth, but the son had always eschewed material possessions and all he had earned had been given away to the poor.

Some weeks later, when he seemed physically no worse, rising very early in the morning he walked from end to end of the huge camp (in which dwelt some 17,000 people) bidding farewell to all he met and blessing them. He then walked about five miles (8 km.) to Jericho, where he had relatives, and repeated his action. Returning to his tent at the camp, where his father sat cross-legged upon the ground, he kissed him and invoked the blessing of Allah upon him; he then lay down with his head in his father's lap and died instantly. Later the boy came to be revered as something of a saint or *welee*.

I hope the Gradgrinds will not try to rationalize these things. Let us recognize that there are still imponderables behind both the jargon and the stupendous achievements of present-day medicine.—I am, etc.,

Southborough, Kent. A. Cameron.

Sir,—As a doctor's wife I am a regular reader of the *Journal*, and was very impressed by Dr. Arnold B. Cowan's letter on premonition of death (*Journal*, September 27, p. 797), because a similar thing happened to my own mother. She was dying of bronchitis and summoned the family round her because she would die that night. I did my best to dispel this idea and said I would see her the next morning. She replied, "You won't. I shall die soon after midnight to-night." She was perfectly lucid, said good-bye to all of us, and asked numerous questions regarding outstanding matters. She died at 12.40 a.m. that night. It is conceivable that one might know one was going to die, but how do such people know when?—I am, etc.,

Gravesend, Kent. Madeline Allen.

Rational Use of Drugs

Sir,—On September 6 (p. 632) you publicized a preparation called "codelprone" in your "authoritative notes" on "To-day's Drugs." Your comment did not in fact go beyond the manufacturer's advertised claims for this mixture of prednisolone, meprobamate, and aluminium hydroxide. Where is the "up-to-date, informed, and expert commentary" (*Journal*, May 3) that we were promised? This is surely just the sort of mixture that should be condemned, a mixture of a drug of proved usefulness, the dose of which is critical, with a drug (meprobamate) which, though widely used, has still to find its place in therapeutics. The trouble with all such mixed tablets is, as has often been pointed out, that the dose of one constituent cannot be altered without also altering that of the others. If there is need for more "spasmolytic action" a larger dose of prednisolone must necessarily be given.

I write as one who is trying to teach the rational use of drugs to medical students and who had hoped that your series "To-day's Drugs" was going to be an innovation that could be recommended to them as a source of critical opinion. My hopes have been largely dashed, although I do not wish to imply that all your reports have been as uncritical as this one. On a number of previous occasions you have cautiously commented in an unfavourable way on polypharmaceutical preparations which are considerably less objectionable than codelprone.

To avoid misunderstanding I would say that I have collaborated in the past and am collaborating now with drug firms in the testing of new drugs, and I recognize the valuable part drug firms play in promoting effective therapy.

If your notes were to become really authoritative, criticism, or lack of mention, would prevent bad preparations from achieving the success which is a tribute to advertising skill rather than to therapeutic efficacy, while favourable comment might lead to your columns being quoted in the advertisements instead of the advertisements being quoted in your columns.—I am, etc.,

London, W.C.1. D. R. Laurence.

Contradictory Statements

Sir,—I should like to draw attention to the following quotations. In the *British Medical Journal* of June 14 an advertisement facing p. 1414 states, "promptly and safely effective, Diamox makes *predictable* diuresis a matter of routine." (Their italics.) The *British National Formulary 1957* (alternative edition) at p. 95 states: "Acetazolamide (Diamox) has proved to be of little value as a diuretic, since its effects are both unpredictable and relatively feeble."—I am, etc.,

Wellington, New Zealand. R. G. Park.

Myocardial Disease of Obscure Aetiology

Sir,—Your brief report of Dr. W. W. Brigden's paper on "Myocardial Disease of Obscure Aetiology" delivered at the Annual Meeting of the B.M.A. in Birmingham, and Professor W. Melville Arnott's comments on the incidence in the Union of South Africa (*Journal*, July 26, p. 234), prompt us to record our experience in Durban. As a preliminary to a full study of the obscure myocardiopathies, we have analysed the case histories of 100 consecutive African patients admitted with congestive cardiac failure to one medical unit, as well as the results of post-mortem examinations of 225 consecutive cases dying from congestive failure. In both series the cause was undetermined in approximately 19%, the frequency of this group being

second only to those cases with rheumatic heart disease and subacute bacterial endocarditis taken together (see table).

	Clinical Material (%)	Necropsy Material (%)
Rheumatic heart disease and subacute bacterial endocarditis	30	27.4
Hypertensive heart disease	18	8.4
Tuberculous pericarditis and constrictive pericarditis	11	12.0
Syphilitic aortitis	8	12.0
Degenerative heart disease	4	4.0
Cor pulmonale	3	15.1
Miscellaneous	7	2.6
Unknown aetiology	19	18.5

Professor Arnott, whom we have consulted, would like to add that his comment regarding the probable incidence of these cases (50%) refers to Africa as a whole, particularly tropical Africa, and not to the Union alone.—We are, etc.,

E. B. Adams.
Durban, South Africa. J. Wainwright.

Convulsions Complicating Anuria

Sir,—Mr. T. F. Redman and Dr. F. M. Parsons (*Journal*, September 13, p. 669) have drawn attention to the supervention of epileptiform fits on the 17th day of an anuric episode and seek an explanation for its occurrence. One pertinent fact emerges. On the 12th day the patient had had administered to her 100 g. of "zeo-carb. 225/Na." On that day she showed a negative balance of water amounting to 370 ml., but thereafter presumably water retention occurred in daily amounts of up to 1,300 ml. for the next four days, when convulsions supervened. Accompanying this retention was a marked fall in the plasma concentration of potassium and of sodium (the latter commencing to rise, however, on the 14th day, reaching approximately normal levels on the 17th). The blood pressure rose steeply on the 17th day—the day that fits supervened.

The exhibition of salt by Dieckmann[1] in the form of intravenous normal saline in a patient in early anuria produced comparable effects, since subsequent to its administration oedema, hypertension, and fits developed. This clinical experience has a counterpart in Hamburger's experimental work,[2] in which by varying the concentration of the extracellular fluid convulsions were precipitated. Seventeen days of anuria may plausibly have heightened the irritability of the cerebral cells. In this connexion it may be worth considering Goldblatt's recent suggestion[3] that under certain circumstances a disturbance of the fluid and electrolyte balance, by some mechanism not yet understood, produces hypertension. In the case described by Mr. Redman and Dr. Parsons the rise in blood pressure was sufficiently marked to be regarded as possibly productive of hypertensive encephalopathy, which Byrom[4] has demonstrated can result from the accompanying cerebral vascular spasm.—I am, etc.,

Worthing. John Sophian.

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Lichen Planus of the Mouth

Sir,—We were interested in Dr. W. W. Gunther's letter (*Journal*, August 2, p. 327) following our paper on "Lichen Planus of the Mouth" (*Journal*, April 26, p. 983), drawing attention to psoriasis involving the buccal mucous membrane. One of the cases we reported also had cutaneous psoriasis and Dr. Gunther wondered whether the mouth lesions in this case were psoriasis. In point of fact this patient did at one time have numerous cutaneous papules of lichen planus in addition to her long-standing typical psoriasis, and the buccal mucous membrane showed the white dots and streaks so typical of lichen planus.

Since our report another of the patients has developed an epithelioma. This case had previously had cutaneous lichen planus, but for 10 years the condition had been confined to the mouth. The epithelioma occurred on the side of the tongue at a site where there was a persistent patch of lichen planus. We have also recently seen another case, not included in the reported series, presenting with an epithelioma on the inner aspect of the cheek, in whom typical lichen planus streaks and spots were present, up to the edge of the neoplasm and also on the opposite cheek and on the lower lip. Neither case had been taking arsenic. We have therefore seen an epithelioma develop in association with lichen planus of the mouth in four patients.—We are, etc.,

R. P. Warin.
Bristol. H. S. M. Crabb.
A. I. Darling.

Road Safety

Sir,—Your correspondent Mr. J. K. Stuart Bell (*Journal*, August 23, p. 512) called attention to the many years' delay in legislation regarding tuberculosis. This is now being stamped out.

I would like to point out another flagrant instance of apathy—that regarding road accidents. These are still increasing and are now the main hazard to life in young men. For instance, in the age group 15–25 there are about 10 times as many deaths from road accidents as from all forms of tuberculosis. And yet one of the main causes of these deaths—drinking in drivers and pedestrians—has been known for years and can be dealt with by legislation. From a local survey of fatal road accidents, already reported in your columns,[1] and since reinforced by similar reviews by the Road Research Laboratory,[2] half the deaths on the road from late accidents, and 10% of all road deaths, are associated with drinking. A speed limit was legalized years ago, and we now need an alcohol limit—a sort of Plimsoll safety-line of alcohol in the system. This will be increasingly necessary as newer and faster roads are built, if we are to avoid the alarming death rates abroad (double ours) in countries where such roads are in being.—I am, etc.,

Leicester. N. I. Spriggs.

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Sir,—The fitting of splash flaps to all road vehicles is a safety measure which has become urgent owing to the higher speed of modern traffic. Stones thrown up by the rear wheels of fast-moving traffic can shatter windscreens and lamps, and damage the paintwork of following vehicles, which are also plastered with mud. Windscreens shattered in this way may be the reason for some unexplained fatal road accidents.

The flaps, fitted behind the front wheels, protect the undersurface of the car from much mud, and those fitted behind the rear wheels provide greater safety, and a cleaner trip, for the cars following behind. Such flaps are compulsory in Sweden for all vehicles, and in Norway for vans and lorries, I understand. The flaps are made in attractive designs carrying the car emblem or name, and some incorporate reflectors on the rear wheel flaps. Should we not follow Sweden's example and have them as a compulsory fitting for road vehicles?—I am, etc.,

Denham, Bucks. J. Myles Bickerton.

Contraception by Inhibition of Ovulation

Sir,—May I reply to some of the points in the letters by Dr. L. M. Franklin (*Journal*, September 20, p. 743) and Dr. G. R. Venning (*Journal*, September 27, p. 796)? I do not wish to do any more than to draw attention to the possibility that substances such as "enavid" may cause foetal abnormalities. It is common experience that substances and methods which have been in use for many years and which have initially been reported on favourably may eventually be condemned as dangerous. Deep *x*-ray

therapy had become well established before Murphy[1] drew attention to the danger to the foetus in pregnant women. It is only very recently that the possible hazards of much smaller doses of irradiation have been appreciated. When studies of new drugs are carried out, there is a tendency to concentrate on the effect on the adult recipient, whilst the possibility of foetal damage may receive little attention. Indeed, resources and opportunities are seldom available to enable lesser abnormalities of the central nervous system such as might result from a disturbance of hormonal balance during pregnancy to be detected. This is particularly so in "underdeveloped countries."

Dr. Venning's contention that the taking of tablets would be discontinued with the onset of pregnancy is hardly valid. The women in the trial were taking 20 tablets during each menstrual cycle, beginning on the 5th day. If a woman were to become pregnant, she would not know this until the end of the cycle at the earliest, in practice often later. There is therefore a considerable risk that the contraceptive tablets would be taken during the critical organo-genetic period of foetal development. Dr. Venning also argues that "natural" substances such as progesterone are less likely to be harmful than "poisons" such as aminopterin. Such a distinction appears a trifle old-fashioned, since it is now known that substances such as aminopterin exert their effect by causing an imbalance of the normal metabolites. Moreover, Millen and Woollam[2] have shown "natural" substances such as vitamin A and cortisone can be markedly teratogenic in excess, whilst Duraiswami[3] has shown a similar action in the case of insulin.

Dr. Franklin is, of course, correct in stating that there is a need to be able to control the size of the family in underdeveloped countries, as also in the more developed countries. There are, however, many neo-Malthusians who over-emphasize this aspect of the difficulties of backward countries and neglect the importance of economic factors.—I am, etc.,

London, S.W.17. BRIAN H. KIRMAN.

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3 Duraiswami, P. K., *J. Bone Jt Surg.*, 1952, **34B**, 646.

Why Are Medical Journals So Dull?

SIR,—I have thought a good deal about Dr. Richard Asher's brilliant article on the subject of medical journals (*Journal*, August 23, p. 502) and have now come to the conclusion that the proportion of its substance capable of undergoing full-scale scientific analysis without refutation is unlikely to be high enough to be of statistical significance; he would probably prefer me to say that a good deal of it is piffle.

A letter cannot, of course, be expected to cover the whole train of reasoning which has led me to this regrettable conclusion, but you may have room for one or two points. First, all journals such as yours must contain a proportion of scientific matter: this, to be of any value to scientists, must be expressed with the greatest possible precision. Hence the necessity for the scientist to write "sucrose" rather than "sugar" when he means sucrose, and "gustation" rather than the obvious alternative suggested by Dr. Asher, "taste," which has, in my dictionary, ten meanings as a noun alone. Again, Dr. Asher has brilliantly exhibited the art of making a statement which has no meaning in such a way that it sounds witty, wise, and incontrovertible. I refer of course to the remark that "ten men cannot write an article any more than ten men can drive a motor-car." It is surely at least equally true to say that one man can no more write an article than he can play a string quartet.

I do agree, however, with the general idea that too many comparatively useless articles are written, especially in specialist journals, and venture to suggest a very simple solution to this problem. If publications are to be considered when medical appointments especially as consultants are made, or when merit awards are allotted, it should be the duty of the assessors to read the publications and to be prepared to bar a man as readily for inflicting dozens of turgid and unreadable papers on his professional colleagues as (and this seems to be the usual policy at present) for being modest enough to publish nothing except accounts of isolated peculiar or interesting incidents, until his experience really justifies it. This would immediately kill the idea that publication is a tedious hurdle that every doctor must surmount, like dissecting a dogfish.

In the matter of presentation, Dr. Asher is a past master of clinical description, and one of the few medical men writing to-day who can provide his readers with the maximum interest and entertainment which can be extracted from his subject; but a really fancy presentation, such as he used so successfully in his "A Woman with the Stiff Man Syndrome" (*Journal*, February 1, p. 265), is necessary only when the substance of the article is of no importance, just as a really fancy label is most useful to a wine merchant in helping him to sell poor stuff.

Briefly, Sir, my feeling in this matter is that certain types of scientific articles are, by their very nature, bound to be dull to anyone not specially versed in the branches of science under discussion; but they are, some of them, very good, and their authors considerately summarize them at the end, and you quite rightly give them pride of place in the *Journal*, reserving space later on for comment of all kinds, and for "General Articles and News," to which Dr. Asher has made such a characteristically outstanding contribution. Piffle it may be, but it was beautifully written.—I am, etc.,

Colchester. J. N. FELL.

SIR,—I read Dr. Richard Asher's article "Why Are Medical Journals So Dull?" (*Journal*, August 23, p. 502) with great interest. In it he quite rightly places the blame for the low standard of articles fairly and squarely on the shoulders of the contributors, but I would suggest that at least part of the fault lies with the journals themselves. Dr. Asher correctly states that articles of a standard which would be rejected by the lay press are often tolerated. The real remedy lies in the hands of the editorial staff, who must bear the ultimate responsibility for the appearance and content of any journal. The situation would be greatly improved if they raised their standards, even at the risk of cutting a swathe through the copious crop of journals medical science sponsors. Indeed, in these days when there is scant leisure for reading, both a diminished frequency of publication and a decrease in the number of periodicals would surely be appreciated.

These remarks are not meant to imply that journals should publish only articles with exceptional literary merit, but that those which do appear should be informative and well written. To-day few articles are considered complete without statistics. As these are not always informative, let alone true to the facts which they are supposed to represent, they could in many cases be disposed of with beneficial results. As Mark Twain wrote: "There are three kinds of lies: lies, damned lies, and statistics." Finally, there is more scope for articles which stimulate ideas on the practical problems which occur in everyday medicine, and they are after all what most readers have to face.—I am, etc.,

Oxted, Surrey. PAUL K. BUXTON.

Medical Education

SIR,—Your account of the conference of the Association for the Study of Medical Education (*Journal*, October 4, p. 851) prompts two comments. Professor G. A. G. Mitchell's remarks about failure rates might well be combined with Dr. J. R. Ellis's upon the Swedish approach: if we examine students after a period suitable to the more able, we shall have a high failure rate; if we allow a period of instruction appropriate to the less able, the brighter students will be encouraged in indolence.

Of multiple-choice questionaries, the virtues are obvious and the vices too little regarded. As Sir George Pickering

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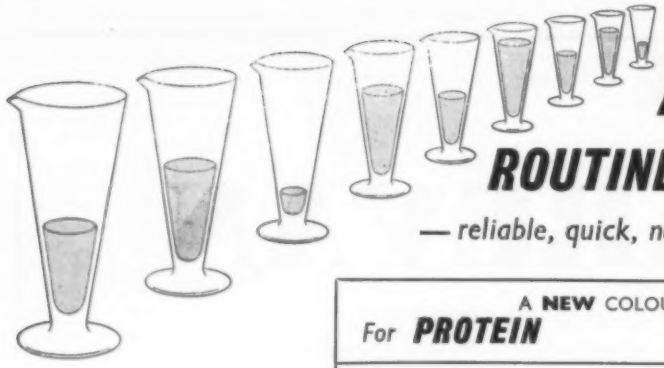

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so pertinently remarked, the form of examinations may determine the students' attitude to their studies. The short answer suggests a premium on factual knowledge, even where in fact the question is designed to test mental abilities. Further, the objectivity of marking suggests a spurious accuracy in assessment which no one claims for the essay question—spurious because it is very hard to be sure that in fact the skills needed to answer such questions are accurately related to the qualities sought in an industrious medical student. We have in this department a growing body of parallel tests upon students by essay question and multiple-choice questionary, which we hope in time to analyse; quite notable discrepancies arise at times, which, in combination with our knowledge of our students, suggest that our questionaries, at any rate, are no panacea to the problems of examination.—I am, etc.,

Department of Physiology, Manchester University. J. N. MILLS.

SIR,—It is probably unfair to judge the value of the first conference of the Association for the Study of Medical Education on the necessarily short report in the *Journal* (October 4, p. 851). Even so, there seems reason to infer that the participants were all living in a Cloud-cuckoo-land. Thus, Sir George Pickering is reported as intimating that "medical faculties were interested not in training the student's mind but rather in his familiarity with the subject and its practical handling." And further on, "While it was nonsense to suppose that the subject-matter of an arts course was inherently more suitable for sharpening the wits than that of a science course, it was true that science faculties, including medicine, were smothering their students with technological detail." Reflection shows that, the more diagnostically and therapeutically efficient medicine becomes, the less it remains a "learned" profession. This is academically sad, but—let it not be forgotten—the State pays the piper of medical education and the State wants competent doctors, not reflective minds capable of "collecting facts, verifying them, arranging them, drawing conclusions, and testing . . . conclusions." Let us be honest with ourselves and ask how many persons on the *Medical Register* would be of greater value to themselves or to the community if they did possess these methodological powers. Indeed, Dr. J. N. Morris's surgeon, called on to deal with a crushed foot, was no better at the job because he was "surprised to find that in many factories there was a kind of collusion between management and labour to ignore safety measures." Sir Russell Brain's antithesis of "safe doctors" and "good doctors" is too vague to be significant: a good doctor must be a safe doctor because the doctor's job is an essentially practical one.

Dr. J. Z. Bowers, dean of the Medical School of Wisconsin, seems to have played an outstanding part in the only reform possible in these busy days: "the preparation of students for medical school had been broadened, the attitude being that science requirements should be held to a minimum . . . and that students should be encouraged to diversify their educational process." Here would appear to be a possibility of enabling the doctor to be an educated member of the community, not *qua* medical practitioner, but as a rounded human being.—I am, etc.,

London, W.1. A. PINEY.

SIR,—By omitting half of one of the statements I made at the recent conference of the Association for the Study of Medical Education (*Journal*, October 4, p. 853) and removing my remarks from their context your report gives a wrong impression. My point was simply that if students are to be taught in the best clinical tradition, by example and experience, about certain aspects of social medicine this will need to be done in people's homes and in the community as well as in the teaching hospital. Such aspects have to do with the education of individuals and families—on smoking, for example, with the earlier detection of disease, the familial repercussions of chronic disease, the continuing care of the chronic sick and the functions of multiple social services, the prevention of admission to hospital, etc. These things are important; and for them to be dealt with on a reality basis will mean extending our teaching outside the hospital. The principle of this is accepted by most medical schools and notably by the Universities of Edinburgh and Manchester.—I am, etc.,

London, E.1. J. N. MORRIS.

Posture and Blood Pressure in Pregnancy

SIR,—I was very interested to read the letter from Drs. P. R. Boucher and Margaret J. Turpin (*Journal*, September 13, p. 693). During the last month I have been treating two pregnant women who had some increase in blood pressure warranting bed rest. Both had only a moderate fall in blood pressure during this time, and it was only after much deliberation that I allowed them up. In both, the following day, there was a considerable fall to normal levels when the blood pressure was recorded in the sitting position. Both these patients, however, had had rauwolfia, and I assumed that the postural factor had been potentiated by this treatment. I wonder if, in view of the possible toxaemia, the reported case had had hypotensive therapy.

Certainly the effect cannot be explained by pressure of the gravid uterus on the great vessels in the lying position, since although the effect is immediate it is maintained, and pressure on both vessels would be more effective in obstructing the flow in the vena cava and give rise to oedema of the legs instead of the relief obtained. Is it possible that the effect could be explained in terms of vasomotor instability causing postural hypotension in individuals with a tendency to this even before they have to cope with the increased circulating volume of pregnancy?

Like Drs. Boucher and Turpin, I am somewhat at a loss to know which figure to regard as the significant one.—I am, etc.,

Harrow-on-the-Hill, Middlesex. K. D. PHILLIPS.

Phenylketonuria

SIR,—I think your annotation on the treatment of phenylketonuria (*Journal*, September 20, p. 736) is a trifle pessimistic. There is still a lot to be learnt about the correct management of patients with this disease. It already seems likely that even with an early start some patients do not improve very much on intelligence and others at the same age do. This is not unlike the situation in cretinism, for, even if thyroid extract given in satisfactory dosage is started early, excellent physical results may be achieved without necessarily raising the mental age high enough for ordinary schooling. (Yet one of the late Dr. F. A. Cockayne's cretins won a scholarship in her "teens"!) Unless a trial is made with a phenylalanine-low diet, it is at present difficult to tell what the response will be. At any rate in young subjects this seems the proper course, although, recently starting treatment late in a girl of nearly 7 years, we think we have pushed her up into the educationally subnormal level. You state: "It seems unfortunately to be the case that by the time phenylpyruvic amentia is established a low-phenylalanine diet is likely to raise a child's mental rating only from idiot to imbecile level, hardly a very gratifying achievement." A child seen since our last paper was completed refutes this. A boy aged 9 months had been attending the Hospital for Sick Children for eczema, and was referred to me for backwardness. My colleague, Mr. Stephen Coates, using the Griffiths scale, made his G.Q. intelligence level only 30 with a wide scatter (that is, almost an idiot). The child was in hospital for six weeks coming under control, and since then has been at home continuously. Six months after discharge his G.Q. was 55 and now at the age of nearly 2½ years it has reached 64, with some indication of levelling out at this point. He will be able to go to an E.S.N. school.

Even if the intelligence level is not satisfactorily raised, the affected children on a phenylalanine-low diet become less restless, more manageable, eczema (if present) improves, and fits (if present) may cease. Thus, when we have proposed stopping the diet to some patients they have begged to be allowed to continue. I feel that if such discouragement as your annotation expresses had been applied to the treatment of cretinism when thyroid extract was first introduced the effect might have been to deny certain cretins a relatively normal life. Ought we not to go on trying a little longer with the phenylketonurics? There is even a faint indication from American sources that tolerance to phenylalanine is acquired and that in some instances perhaps the diet may be discarded when the child reaches the "teenage."—I am, etc.,

London, W.C.1. ALAN MONCRIEFF.

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Depressive States

SIR,—Dr. Robert Thompson (*Journal*, August 23, p. 510) asks "what can one give" to depressive cases if E.C.T. is withheld? The answer is the amphetamine group, the dose being dependent upon the patient and the preparation. Amphetamine sulphate is about one half as effective as desoxyephedrine or methylamphetamine.[1 2]

In a comparison of the two treatments in recurring attacks of depression in the same patients, I found[3] that, in 20 cases who were treated in 58 attacks, improvement occurred in different attacks with either E.C.T. or methylamphetamine in 14 cases; with E.C.T. but not with methylamphetamine in one case and with the reverse in three cases. Two cases showed no benefit from either treatment. One case treated in each of nine attacks showed improvement with E.C.T. in five attacks and with methylamphetamine in four.[4] Subsequently he kept the preparation with him, warding off the attacks as they came. Comparison of mild cases treated by myself with E.C.T., 30 cases, or methylamphetamine, 42 cases, gave similar improvement rates of about 80% with each treatment,[5] the oral methylamphetamine being used in doses of from 1.25 to 60 mg. daily, the larger quantities being divided into three doses before 1 p.m.[6] Monro and Conitzer[7] treating depressives in a mental hospital and not exceeding one half of my maximum dosage of methylamphetamine, found 34.5% improvement in 34 cases, but 78.1% in 200 cases with E.C.T. No marked improvements, and double the rate of slight improvements as with E.C.T., were obtained with this low dosage of methylamphetamine and with mental hospital patients.

A summary of the literature showed that of 1,616 cases, of all types of depression, marked improvement occurred in 63.9% with E.C.T. and in 33% with methylamphetamine.[4] No improvement was seen in 8.7% treated with E.C.T. and in 23.4% with methylamphetamine. Somewhat similar results were found in involutional, manic, and anxiety depression, but reactive depression gave 53.3% marked improvement with methylamphetamine, and only 34.7% with E.C.T.

Although Dr. Gerald Garmany (*Journal*, August 9, p. 341) and Dr. Robert Thompson feel that no types but only degrees of depression exist, I have treated, with improvement, a patient whose constant level of depression was improved with ethisterone, but whose sudden attacks of more severe type were abolished by amphetamine. This one patient shows two types of depression relieved by different methods. In view of the distressing amnesia and other risks associated with E.C.T., I would like to suggest strongly again that, except in severe or suicidal cases, amphetamine should be tried initially, as marked improvement may be obtained with this treatment without resorting to the more inconvenient and serious electric convulsive therapy.—I am, etc.,

Clevedon, Somerset. G. DE M. RUDOLF.

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3 Rudolf, G. de M., *Practitioner*, 1955, **174**, 180.
4 —— *J. ment. Sci.*, 1956, **102**, 358.
5 —— *Lancet*, 1955, **1**, 1178.
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7 Monro, A. B., and Conitzer, H., ibid., 1950, **96**, 1037.

Iatrogenic Disease in Childhood

SIR,—I was pleased to read the report of Dr. A. White Franklin's address "Iatrogenic Disease in Childhood" (*Journal*, August 30, p. 559) because it draws attention to some undesirable features of our present medical practice. The child who undergoes a tonsillectomy or circumcision which might well have been omitted, or the child subjected to repeated painful procedures for some mild self-limiting disease, does not quickly forget. But the worst procedure of all was never mentioned—that is, the injection of radioactive materials into the body. What gives us the impression that "there's no real harm in it" when at the same time luminous watches and the shoe-fitting fluoroscopes are under suspicion as potential dangers? Is it not believed that there is no threshold for some of the harmful effects of ionizing radiations?—I am, etc.,

Aylesbury, Bucks. J. VACCARO.

Psychiatric Illness Among Asian Students

SIR,—Like Dr. M. N. Pai (*Journal*, September 13, p. 689), we have seen a number of Asian students with mental illness in the department of psychiatry of Manchester University. I am surprised he does not mention obsessional neurosis. The illness often takes the form of paralysing doubt which stifles any form of original thinking and brings the patient's work to a standstill. It occurs in men of basically insecure character—anankastic in Schneider's classification[1]—and its development is favoured by the cultural, social, and sexual problems posed by Western society. The change from their own community, with its rules of endogamy and fixed social-religious order, to an open society with freer relationships between the sexes seems to be responsible. Many have distinct feelings of inferiority and hostility towards English people. A satisfactory doctor–patient relationship in psychotherapy is thereby prejudiced, and a notoriously intractable illness is rendered even more difficult to treat.—I am, etc.,

Manchester, 13. LINTON GRIMSHAW.

REFERENCE

1 Schneider, K., *Psychopathic Personalities*, 1958, translated by M. W. Hamilton, London.

Buzzers for Bed-wetters

SIR,—I wish to support the plea of Dr. D. Saklatvala (*Journal*, September 13, p. 690) for more humane means of treating bed-wetting. Since the great proportion of cases are psychoneurotic in origin, more investigation into the treatment of the underlying mental condition should be made. Waking the child up with buzzers will further exacerbate any emotional difficulties, since the child will be less able to cope with them through lack of sleep, and may lay the foundations for further hysterical or other phenomena.

Dr. Saklatvala's letter also gives a clue to the aberration responsible; the child has an aversion to water. This will give him a feeling of being short of something vitally necessary for life; his body will store up water during the day; and, when his subconscious control is relaxed in sleep, water will flood out of the tissues and be excreted into the bladder. The fears of the daytime will lead to an undue relaxation at night owing to exhaustion, and bed-wetting will result. This is exacerbated and perpetuated by starving the child of fluids at night.

I have never been disappointed in the general improvement in health and cure of this trouble after telling the parents to load the child with pints of fluid at all times during the day. It is difficult to persuade the parents to cooperate, but it can be done.—I am, etc.,

Reading. G. H. GILFORD.

SIR,—I hasten to reassure Dr. P. Saklatvala (*Journal*, September 13, p. 690) that he is mistaken in assuming that "subtle unkindness" is implied in the management of nocturnal enuresis by a buzzer technique. Rather, orthodox

management based upon fluid restriction, the exhibition of drugs which have side-effects, and arbitrary lifting at times when there is no conscious or unconscious desire to micturate seems not only "unkind" but calculated to perpetuate the disability by conditioning.

It is apparently not generally realized that the buzzer method of management does *not* train the child to awaken in response to impulses centrally received from the bladder but the diametric opposite—namely, to sleep continent and undisturbed throughout the night. Further, no fluid restrictions are placed upon the child either during or after treatment. Mowrer and Mowrer,[1] in reviewing a large series of enuretics treated by a "buzzer-like" method, stated that "personality changes when they occurred have universally been in a favourable direction." I am not aware of any published refutations of this observation. Finally, I wonder whether Dr. Saklatvala still persists with his plea for "more patience and less drama" when dealing with enuretics in the age group of 14–21 years.—I am, etc.,

Ilkeston. J. L. SKINNER.

REFERENCE

1 Mowrer, G. H., and Mowrer, W. M., *Amer. J. Orthopsychiat.*, 1938, **8**, 436.

Miners' Nystagmus

SIR,—I was interested in your leading article (*Journal*, September 20, p. 732) because in America, where lighting in mines is good and the central helmet lamp is universally used, the general opinion in 1948 was that no problem existed. As you say of this country, "miners' nystagmus has certainly decreased since the introduction of better illumination in mines."

Regarding a few other points: (1) That sufferers from the disease are less emotionally stable than those without, is surely to be expected. Bad lighting increases anxiety and stress, and the unstable show the symptoms first. (2) In the years 1930–3 the importance of working was paramount: none could afford sickness. They were driven by want. The number affected therefore decreased. (3) In the last world war men became exhausted, safety precautions were sometimes neglected and overlooked, and danger suspected in the dark is worse than danger seen. Money was abundant and work not imperative. The numbers therefore increased. (4) Every man has his breaking point and even a little stress endured for a lifetime may ultimately produce symptoms. It is worth considering that where a defect is socially acceptable and widely known there is apt to be hysterical contagion.—I am, etc.,

Farnham Royal. M. E. M. HERFORD.

Mind the Zip

SIR,—A boy of 8 was brought to the casualty department with his foreskin caught in the zip fastener of his trousers. An attempt to release the foreskin by moving the slide of the zip only resulted in jamming the foreskin more tightly into the zip. Efforts to dismantle the zip were unsuccessful until it was found that, by cutting it across with scissors just below the place where it emerged from the slide, the slide could be removed quite easily, releasing the imprisoned foreskin.—I am, etc.,

Portsmouth. D. L. HADLEY.

POINTS FROM LETTERS

Thoracic Outlet

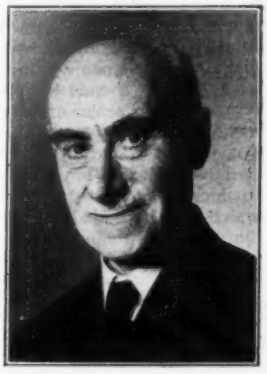
Dr. M. B. LEITCH (Carluke, Lanarkshire) writes: The term "Thoracic Outlet Compression Syndrome" used in the article by Professor C. G. Rob and Mr. A. Standeven (*Journal*, September 20, p. 709) is surely a misnomer. Is not the "outlet" of the thorax generally considered to be at the *lower* end: the upper end is the inlet. This may seem a trivial point, but it is one which leads to confusion when a patient is sent for *x*-ray examination of the thoracic "outlet."

Obituary

D. N. NABARRO, M.D., F.R.C.P.

Dr. David Nabarro, consulting pathologist to the Hospital for Sick Children, Great Ormond Street, London, died at his home in London on October 3. He was 84 years of age.

David Nunes Nabarro was born in London on February 27, 1874, and was educated at Owen's School in the City. He entered University College, London, with an Andrews scholarship, and from there went on to University College Hospital to receive his clinical training. He qualified M.R.C.S., L.R.C.P. in 1897, having previously taken the London B.Sc. in 1893 at the age of 19. He then obtained the London M.B. in 1898, having gained the Fuller exhibition in pathological anatomy and pathology, and proceeded to the M.D. in the following year, winning a gold medal for his thesis and the Clothworkers' Company's exhibition. Elected a Member of the Royal College of Physicians of London in 1901, the year in which he took the D.P.H. of the English Royal Colleges, he became a Fellow of the College in 1917. After holding the appointments of demonstrator of physiology and histology at University College and house-physician at University College Hospital, a period as a ship surgeon followed. He then returned to London and was assistant professor of pathology and lecturer in bacteriology at University College from 1899 to 1910. In 1900 he was elected a Fellow of the College, and at the time of his death was senior Fellow jointly with Professor M. W. Travers. In 1901–2 he was pathologist to the Evelina Hospital for Sick Children. Appointed a member of the Royal Society's commission on sleeping sickness in Uganda in 1903, he was the joint author, with Sir David Bruce, of the first, fourth, and fifth reports. With Sir David Bruce and Dr. Aldo Castellani he discovered the cause and mode of transmission of the disease. In 1907 he translated and edited Laveran and Mesnil's book, *Trypanosomes and Trypanosomiases*. He was awarded scientific grants by the British Medical Association in 1905 and 1906 to help him conduct an "investigation of butter and butter substitutes for the presence or absence of the *B. tuberculosis*."



After a brief period as pathologist to the West Riding Asylum, Wakefield, Dr. Nabarro returned to London in 1912 and was appointed clinical pathologist to the Hospital for Sick Children, subsequently becoming director of the pathological department and medical officer in charge of the venereal diseases department. He retired in 1939. During his many years at the hospital he conducted an investigation of Sonne dysentery, following his work at Wakefield; he initiated the first children's venereal diseases clinic in 1917; and he started the biochemistry department in 1923. Other work at the hospital included the preparation of measles serum and its utilization, and the treatment of infantile general paralysis of the insane. For some 20 years from 1904 he was scientific assistant in pathology in the University of London.

He wrote many articles for the medical and scientific journals. Before he qualified in medicine he contributed an article to this *Journal*, jointly with Dr. (later, Sir) Leonard Hill, on the exchange of blood gases in brain and muscle in

states of rest and activity. At the age of 80 he produced a book entitled *Congenital Syphilis*, which ranks as a classic. He was a founder-member and a past-president of the Medical Society for the Study of Venereal Diseases; a past-president of the Association of Clinical Pathologists and the London Jewish Hospital Medical Society; an honorary member of the British Paediatric Association; and a corresponding member of the Société de Pathologie Exotique of Paris. He was also the senior member of the Pathological Society of Great Britain and Ireland. A member of the British Medical Association for nearly 60 years, he served as a vice-president of the Section of Pathology and Bacteriology when the Association held its Annual Meeting at Manchester in 1929. His hobbies were gardening and philately, in which he was an acknowledged expert on the stamps of the Falkland Dependencies. He married Miss Florence Nora Webster in 1914 and had one son and one daughter.

We are indebted to Mr. T. Twistington Higgins for the following appreciation: The death of David Nabarro removes from Great Ormond Street a familiar and universally beloved figure, and from British paediatrics a pioneer whose name will long be held in honoured memory. To his many friends his passing, even at a ripe old age, brings a deep sense of personal loss, for he was a most lovable character whose sprightly companionship endured. For me his friendship has been a treasured privilege for wellnigh half a century. Nabarro came to the Hospital for Sick Children in 1912 to concentrate on child pathology, which then included the growing science of bacteriology and was soon to incorporate biochemistry. His credentials were brilliant, his experience extensive, varied, and picturesque. The highest professional appointments were clearly within his scope, yet the potentialities of paediatric pathology lured him and at Great Ormond Street he found his *métier*. In accommodation which was far from palatial and on a salary which was certainly not princely, he built up a department unrivalled in its day and a reputation which will not fade.

Nabarro was extremely accurate in all his work; any report franked "D.N." was utterly reliable. Tireless in his devotion, the little white-coated figure, bristling with the armamentarium of his specialty and bustling around usually at the double, became a familiar feature of the wards; and the well-ordered "lab" in the bowels of the ancient building was the Mecca to which all problems could be taken with the certainty of a warm welcome and wise informed guidance. Colleagues trusted him implicitly, children loved him instinctively. In his gentle and wonderfully skilful hands even the dreaded needle lost its terrors. How much is owed in this respect alone to the standards of technique set by Nabarro! An early ploy was the institution of the clinic for syphilitic children which he ran himself. He did his own serology, and the weekly "Wassermann night" was an event which tended to disrupt the residents' evening meal—especially if things went wrong. The increasing lateness of the hour of his departure for home was a measure of the rapid expansion of the clinic's clientele. Congenital syphilis became for Nabarro an absorbing interest by no means confined to its clinical and serological fascination, but also in its sociological and humanitarian bearing. Many a mother tasted the milk of his human kindness. His book, based on a wealth of experience, now happily unrepeatable, will remain a gold-mine of reference.

But David Nabarro was no one-track man. His interests were many, his mind cultured. Widely travelled, an accomplished linguist and littérateur, and a lover of classical music, he was a delightful companion on a country walk or as host at his own table. No one could be a more stimulating and loyal friend. His home life was entirely happy, and he and his wife were rewarded deservedly in the achievements of their children. All who knew him best will share the sincerest sympathy for them at this time. Few men carry with them to the Great Beyond a richer harvest of the things that matter than David Nunes Nabarro.

B. E. S. writes: David Nabarro's death severs one of the last links with the great masters of Great Ormond Street in the early part of this century. During the years he worked at the hospital he saw many generations of young doctors pass through their training and a number graduate to the staff and become his colleagues. He was beloved by all, because his warm character, enthusiasm, and understanding eventually attracted everyone, even those who at first thought him rather an odd little figure as he scurried down the underground passages of the old hospital, for all the world like the White Rabbit in *Alice in Wonderland*. But Nab was always ready to help and advise young housemen and other members of the staff with wisdom, based on long experience, yet great enough to have visions of the future. The hospital will always be grateful to his energy and perspicacity, which gave birth to the pathological department under his guidance as its first director. Apart from routine work he had many interests. Research into the spread and prevention of dysentery, the supply of pure milk, and many other activities occupied his time, but he became best known to the outside world through his studies of congenital syphilis. This culminated in his *magnum opus*, which, like that of Verdi, appeared towards the end of his life. For years he had run a clinic dealing with this disease and was in charge of a ward tucked away so far from the rest of the hospital that the loneliness of the night nurses presented quite a problem. As a young man he was a member of the commission which went to Uganda to study trypanosomiasis, and it is probably true that he never received the recognition due to him for the discoveries made at that time. But he was modest, retiring, and not one to fight for his own rights, although always ready to champion those of others. He was a good example of a little man with a great heart. His old hospital and the pathological world will undoubtedly miss that familiar figure, and his many friends will always have their pleasant memories and smilingly venerate his name.

MARIE C. STOPES, D.Sc., Ph.D.

Marie Carmichael Stopes, D.Sc., Ph.D., noted for her pioneer work as an advocate of contraceptive practices in married life, died on October 2, aged 78. Marie Stopes's early books, published immediately after the first world war, discussed contraceptive techniques and the physical aspects of marriage with a candour unknown in those days, and her views and manner of expressing them were the cause of strong protest. Her books achieved an enormous circulation among ordinary people, to whose needs they appealed and for whom they were largely written. She started birth-control clinics in London, Leeds, and Aberdeen, and others inspired by her work also founded clinics. These eventually became united under the Family Planning Association.

Marie Stopes was by training a botanist. She gained the gold medal in junior and senior botany at University College, London, and took her B.Sc. and later her D.Sc. She graduated Ph.D. at Munich. In 1904 she became the first woman to be appointed to the scientific staff of Manchester University. In 1907 she went to Japan and during a year and a half at Tokyo University explored the country for fossils. She returned to Manchester as a lecturer in fossil botany. She was a fellow and sometime lecturer in palaeobotany at University College, London.

We are indebted to Mr. Aleck Bourne for the following appreciation:

Dr. Marie Stopes had lived for more than 30 years before she devoted her energies to the propagation of knowledge of the control of conception. Though she was not a member of the medical profession she has contributed indirectly to the medical problems of pregnancy and labour complicated by certain associated diseases. At the University of London she graduated as a Doctor of Science with first-

class honours and a gold medal. Her chief interests during her earlier years were the study of the fossils of plants, which gained her election to the Geological and Linnean Societies and a reputation far beyond this country. Dr. Stopes worked first in London, then in Munich, where she took the Ph.D., and in Berlin, Japan, and Manchester, where she was appointed to a lectureship in palaeobotany, on which, by her scientific papers, she became a recognized authority. The unfortunate experience of her first marriage, annulled on account of its physical failure, turned her attention to the problems of marriage and thus to the prevention of conception by the use of an obturator by the woman. Though other contraceptive methods had been practised for many years, her missionary zeal in publicizing her technique excited the massive opposition of orthodoxy, partly on religious grounds and perhaps more by her defiance of popular disapproval of public discussion of intimate sexual details. But Marie Stopes became a passionate pioneer and therefore a rebel against the established prejudices of the time.

Unlike the reformer in the fable by R. L. S. who "preached under the tree at noonday and was buried at dusk," she escaped the usual fate of a pioneer and pursued her mission with the courage that flourishes on antagonism. In 1918 she published her first book, *Married Love*, which dealt more with the difficulties of some marriages than with contraception, and later in the same year a forthright appeal for "birth control" in *Wise Parenthood*. She exposed the strain caused by the unwanted child, a yet further addition to a family already worried by economic difficulties, which could be avoided by the voluntary spacing of the children, whereby each birth would be welcomed. *Married Love* commanded an instant and enormous success because it was an entirely new presentation of some of the problems of difficult marriages and written in simple unscientific language which ordinary people could understand. In 1921 Dr. Stopes and her second husband devoted their own resources and the royalties accruing from her books to opening the "Mothers' Clinic for Constructive Birth-Control" in North London. This was the first clinic of its kind to be established in this country and probably the world. Other clinics rapidly followed, until now there is no large town without its consultative centre. Following her example other independent enthusiasts set up their own clinics which were united under the "Family Planning Association," but Dr. Stopes was a dominating personality who could not accept co-operation with other organizations in which she played no part. Nevertheless the association, inspired by her work, has developed into a national institution which now gives advice and practical help not only to women who desire to limit their families but also to those who are distressed by infertility. Slowly but with increasing conviction the whole world is coming to realize that, unless the growth of its population, now increasing at an alarming geometrical rate, can be controlled, it will, within measurable time, outstrip available food supplies, and by its national pressures, especially in Asia and Africa, ultimately lead to wars of expansion in relatively empty countries.

Dr. Stopes, far beyond her original mission, has led the way to a hoped-for solution of these world problems by focusing attention on the control of excessive births and, indirectly, stimulating research on the techniques of contraception. Though not strictly a disciple of Malthus, for she was concerned with the individual woman and family, her emphasis on the necessary control of conception may, and probably will, make it possible in future years to limit the population of the world to an optimum figure.

CHARLES M. FRIER, M.B., C.M.

Dr. Charles Frier, a Fellow of the British Medical Association, and well known at Headquarters as a representative at the Annual Representative Meeting over a very long period, died at his home at Grantham on September 24. He was 87 years of age.

Charles Matthew Frier was born on January 15, 1871, and was educated at Edinburgh University, where he graduated M.B., C.M. in 1892. After graduation he held the appointments of assistant house-surgeon at the Coventry and Warwickshire Hospital, house-surgeon at the Royal Surrey County Hospital, Guildford, and resident medical and surgical officer at Jaffray Hospital, a branch of the Birmingham General Hospital. A period as a ship surgeon followed before, in 1896, he settled in general practice at Grantham, where he remained for the rest of his life. For many years he was also surgeon to the Grantham and District Hospital. In the affairs of the British Medical Association Dr. Frier had an outstanding record. A member for fifty-nine years, he was first elected the representative of his Division at the Annual Representative Meeting in 1913, and from that year until 1953 was returned in a similar capacity on thirty-six occasions. He became the first president of the Lincolnshire Branch when it was formed in 1932, and previously he had been chairman and honorary secretary of the Kesteven Division. Earlier this year he was admitted to the newly established Roll of Fellows of the B.M.A. in recognition of his long service to the Association. He had also been a member of the Conference of Local Medical and Panel Committees for many years since its inauguration. He served on the Kesteven Executive Council for some time, and was honorary secretary of the Lincoln (Kesteven) Local Medical Committee until 1954. Dr. Frier was a popular member of the medical fraternity in Grantham and district, and in course of time came to be regarded as the friend of all and as one from whom guidance and help was to be had for the asking. He will be very much missed by his colleagues, his friends, and his former patients.

K. V. TRUBSHAW, M.B., F.R.C.S.Ed.

Mr. K. V. Trubshaw, for many years honorary surgeon to Chester Royal Infirmary, died on September 15, at Dolgellau, Merionethshire, where he had been living in retirement. He was 81 years of age.

Kenneth Vincent Trubshaw was born on December 22, 1876, the son of Dr. Alfred Trubshaw, and was educated at Epsom College. Receiving his clinical training at Guy's Hospital, he graduated M.B., B.S. from London University in 1901. He was elected F.R.C.S.Ed. in 1918. After graduation he held the appointments of house-physician to Sir Frederick Taylor and clinical assistant and house-surgeon to Sir Arbuthnot Lane at Guy's Hospital. Following a period as a ship surgeon, he joined his father in 1904 in general practice at Mold, Flintshire, where he remained until 1919. During the first world war he could not be released for military service, and conducted three men's practices single-handed. During this time he was in charge of Leeswood Hall military orthopaedic hospital, where he came into close contact with the late Sir Robert Jones and Dame Agnes Hunt. From 1919 to 1930 he was honorary surgeon on the staff of Chester Royal Infirmary. After leaving Chester he went to live at Dolgellau, and was appointed consultant surgeon to the local hospital, which received the benefit of his skilled service almost daily until 1939, when he was succeeded by Lieutenant-Colonel H. Bodley Scott, who outlived him by only five days.

R. W. E. and H. D. O. write: In the passing of Mr. K. V. Trubshaw the profession has lost a specialist who possessed an all-round knowledge of every branch of medicine—a rarity in this age of "watertight compartments." His experience in general practice served him well later as a surgeon. He was never in a hurry and his approach to a patient was always calm and modest, and so he gained the complete confidence of all concerned. His extreme care and consideration of every surgical problem gave him a clear concept of treatment and a high efficiency as an operator. He possesed a boundless energy. A keen athlete and sportsman, he had distinguished himself as a cricketer and, Rugby player in his earlier years and continued to play tennis with vigour to the age of 65. When not engaged with

his professional work, he enjoyed occupying himself in his workshop and garden. A skilled mechanic, his handling of all sorts of tools and instruments was exceptionally dexterous. He was a very loyal colleague and maintained the highest traditions of the medical profession. He is survived by his wife and three daughters, who nursed him with loving and tender care during his last illness, and to them we extend our sympathy.

H. BODLEY SCOTT, O.B.E., F.R.C.S.Ed.

Lieutenant-Colonel H. Bodley Scott, formerly professor of surgery in the University of Rangoon, died at his home at Dolgellau, Merionethshire, on September 20. He was 75 years of age.

Herbert Bodley Scott was born on December 14, 1882. He received his medical training at St. Bartholomew's Hospital, and qualified M.R.C.S., L.R.C.P. in 1904. He was elected F.R.C.S.Ed. in 1923. After qualification he held the appointment of assistant house-surgeon at Salisbury Infirmary. In 1907 he entered the Indian Medical Service, in which he served for over 30 years, retiring with the rank of lieutenant-colonel in 1939. He was appointed O.B.E. in 1921 for services rendered during the operations in Waziristan. He is survived by his only daughter, to whom our sympathy is extended. Mrs. Bodley Scott died in 1956, and his only son was killed in 1940 while on active service in the second world war.

R. W. E. and H. D. O. write: Lieutenant-Colonel H. Bodley Scott from the start of his career took an active interest in surgery, and his success in this field led eventually to his appointment to the chair of surgery in Rangoon University, where he was held in high esteem both by his colleagues and by his students. He served throughout the first world war with an Indian cavalry regiment in Egypt and Mesopotamia. After his retirement from the I.M.S. he went to live at Dolgellau, and was appointed consultant surgeon on the staff of the local hospital, succeeding Mr. K. V. Trubshaw, who died only five days before he did. At the hospital he willingly gave his services and proved himself to be a first-class surgeon. Somewhat reserved and most discreet, he was courteous in his dealings with patients and staff. His military career had made him a man of action and few words, and to the end he led a busy life, keeping himself fully occupied in various pursuits around his country home.

W. H. LASLETT, *M.C.*, M.B., Ch.B.

Dr. W. H. Laslett, who was in general practice at Farnworth, near Bolton, for over 40 years, died at his home there on September 6 after a long illness. He was 69 years of age.

William Henry Laslett was born on January 30, 1889, the son of Dr. T. G. Laslett, and was educated at Hutton School and at the Victoria University of Manchester, where he graduated M.B., Ch.B. in 1911. After graduation he held the appointment of house-surgeon at Rochdale Infirmary and St. Mary's Hospital, Manchester, before joining his father in general practice at Farnworth. After the outbreak of the first world war in 1914 he volunteered for service and was drafted to the South Staffordshire Regiment, and was mentioned in dispatches while in Gallipoli. Later, when a captain in the R.A.M.C. attached to the Royal West Surrey Regiment in France, he was awarded the Military Cross in 1918. At the end of the war he rejoined his father in practice. The extra work during the last severe influenza epidemic in all probability aggravated his illness. He was a very reserved man, hating publicity. He was a vice-president of the local amateur dramatic society and was also interested in chess, photography, and sport. Our sympathies go out to his widow and two daughters, and to his son, who is carrying on the practice.—J. F. S.

Sir BENNETT HANCE, K.C.M.G., K.C.I.E., O.B.E. M.D., F.R.C.S.Ed.

H. H. E. writes: I would like to add a few words to the excellent obituary of Sir Bennett Hance which appeared in the *Journal* of September 20 (p. 745). Before the first world war, at Guy's Hospital, he was a popular, colourful personality, very much the leader in his "firm." We met again after the war on the North-West Frontier of India, where he was a civil surgeon and I was still on the military side. We collaborated in all the surgery there, and he was a stimulating person to work with, full of ideas and anxious to try new treatments. In addition to being civil surgeon he was superintendent of the local jail. At midnight in the middle of the hot weather he rang up and asked me to go with him to the jail, where rumour stated that irregular practices were being carried out. We found nothing, but the fact that the superintendent could visit the jail at that time of night certainly shook the staff and kept them on their toes. "J. B." (as he was called) told us once that when working in Vienna on one of his study leaves he had been psycho-analysed by Freud. I wonder if that experience had anything to do with his poise and zest? His innumerable kindnesses to young officers and others, both British and Indian, will never be known by other than the recipients—none of them could do anything to repay his kindness—but I am sure all retain happy memories of a delightful personality.

Medico-Legal

TRAUMA AND SARCOMA

On July 4 William Nunn, aged 49, a cowman, died in the Ipswich and East Suffolk Hospital from a metastasizing fibrosarcoma of his right femur. Four years previously he had been violently kicked by a cow just above his right knee, and at the inquest into his death, held by the Ipswich coroner, medical evidence was offered as to the relevance of this accident to the development of the sarcoma.

Kicked by a Cow

On a morning in October, 1954, Nunn was assisting the head cowman at Capel Hall Farm, Trimley St. Martin, where a herd of 65 cows was being tuberculin-tested in the milking parlour. Nunn walked up to the left side of one of the last animals to be tested, in order to remove a chain from a post near the cow's hind legs and attach it to another post. As he was fastening the chain the cow lashed out and gave him a very violent kick just above his right knee-cap so that he was knocked against the wall. He hobbled about until lunch-time, but left work then and did not return for some days. When he came back, the head cowman said Nunn showed him a "terrific bruise" just above his knee. Subsequently Nunn complained to him of pain in his knee after heavy work and in the second year sometimes of pain in the groin; occasionally his knee swelled up. Nunn's wife said they called in the doctor the day the accident occurred, but, despite treatment with a lotion, the knee remained always uncomfortable. Because of this and a recent increasing swelling around the knee he was sent in January, 1957, to an orthopaedic surgeon at the Ipswich and East Suffolk Hospital. There was then a swelling involving the lower part of the shaft of the right femur. On biopsy sarcoma was diagnosed and the leg was amputated through the upper part of the femur. Pathological examination of the femur showed a spherical tumour at its lower end 5 in. (12.7 cm.) in diameter, with the appearances of a fibrosarcoma. There were pathological fractures in the bone, but the exact site of origin of the tumour could not be determined.

Nunn made a good recovery from his operation, but by October secondary deposits were apparent in his chest. In February, 1958, a lump appeared in his right groin. He

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was seen by the radiotherapist, but, as there were no symptoms, he was not given *x*-ray treatment. By June a large secondary deposit in the right lung was pressing on the mediastinum and he had palliative radiotherapy. He died on July 4.

Medical Opinion

At the inquest the orthopaedic surgeon, the radiotherapist, and the pathologist concerned in the case all gave their views on the possible relationship of the kick to the development of the fibrosarcoma. The surgeon said it was a fairly uncommon tumour. He had not seen many similar cases, but the lower end of the femur was the commoner site for the tumour. He knew of one recent case where injury and infection had preceded the growth, but it was impossible to say definitely whether the kick had caused Nunn's growth; equally it was impossible to deny that it might have done so. However, his own view was that it was more than a coincidence that the tumour had developed at the site of the kick. It had been a severe blow, and so far as could be seen the tumour had arisen at the exact site.

The radiotherapist said that, while medical opinion held generally that a causal connexion between trauma and tumour development was strongly improbable, it could not be excluded in a particular case. The pathologist thought most of the evidence was against such an association. There did occur, however, occasional cases in which a sarcoma appeared a few months or years after an injury to the bone at the particular site. This might be a chance association, but there were cases—though rare—in which the relation to injury appeared well established.

A verdict of accidental death was recorded.

Vital Statistics

Poliomyelitis Vaccine

By October 3 last 17.5 million doses of poliomyelitis vaccine had been distributed in Great Britain since the programme started in 1956. Of these, 5.7m. were British, and 11.8m. Salk-type. Up to the end of August 5.8m. children and adults in priority groups had received two doses of vaccine, and the number of doses then held in stock by local authorities was 3.2m. The Ministry of Health is recommending parents to avoid delay by accepting whatever vaccine is available locally.

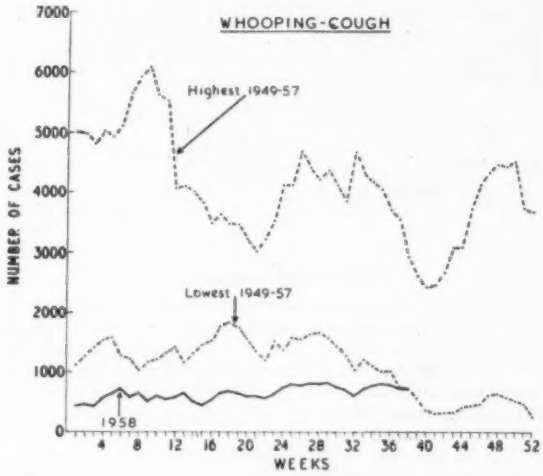
Scotland in Second Quarter

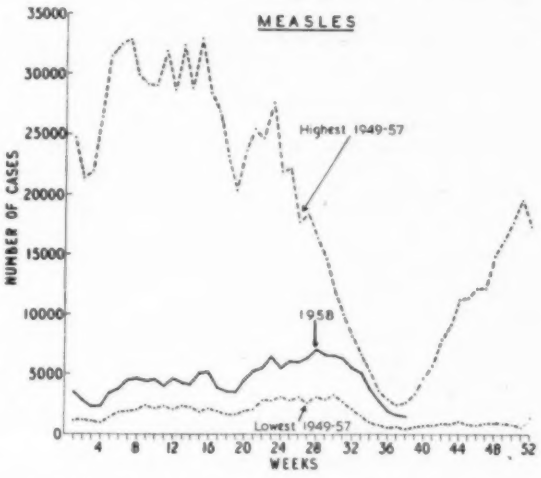
The birth rate in Scotland during the second quarter of 1958 was 19.9 per 1,000 of the population, and was 0.4 above the rate for the preceding second quarter. The infant mortality rate was 27 per 1,000 registered live births, which was the same as in the corresponding quarter of 1957. The neonatal mortality rate was 19 per 1,000 live births, and was 1 below the rate for the preceding second quarter. The crude death rate was 11.8 per 1,000 of the population; this was 0.6 higher than in the second quarter of 1957 and 0.4 above the average of the corresponding quarters of the five previous years.

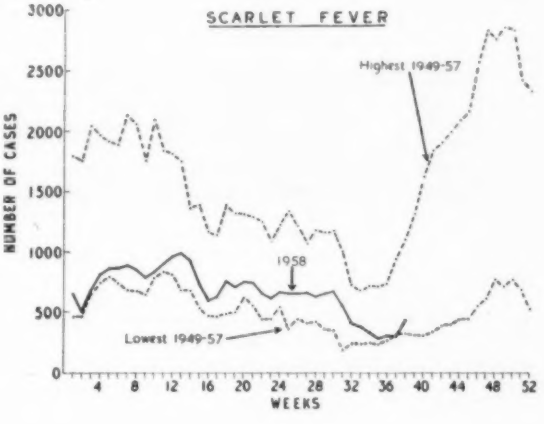
The mortality from bronchitis and pneumonia was high, with death rates of 34 and 37 per 100,000 of the population, respectively, compared with the average rate for the five previous years of 30 in each case. The number of deaths from tuberculosis was 118 for the respiratory system and 16 for other forms. Compared with the preceding second quarter these deaths were 20 fewer for respiratory tuberculosis and 1 more for other forms of tuberculosis. The 43 deaths attributed to the principal epidemic diseases included 36 from influenza, 6 from meningococcal infections, and 1 from measles. Deaths from violence numbered 667. Of these, 137 were due to road transport accidents. These deaths were 27 and 11, respectively, more than in the corresponding quarter of 1957.

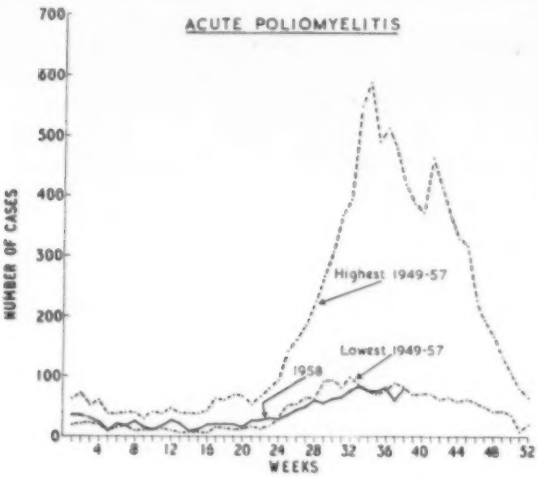
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ———. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending September 27

The largest fluctuations in the notifications of infectious diseases in England and Wales during the week ending September 27 were increases of 151 for measles, from 1,470 to 1,621, 109 for scarlet fever, from 434 to 543, 23 for dysentery, from 410 to 433, and decreases of 47 for whooping-cough, from 718 to 671, 22 for food-poisoning, from 369 to 347, and 21 for acute pneumonia, from 175 to 154.

The largest rise in the incidence of measles was 39 in Gloucestershire, from 38 to 77. A small rise in the incidence of scarlet fever was recorded throughout the country; the only large rise was 42 in Lancashire, from 53 to 95. The only fluctuation of note in the local trends of whooping-cough was a fall of 25 in Sussex, from 40 to 15. Two cases of diphtheria were notified, being the same number as in the preceding week.

The notifications of acute poliomyelitis numbered 95, and these were 6 more for paralytic and 10 more for non-paralytic cases than in the preceding week. The largest returns were Yorkshire West Riding 16 (Leeds C.B. 4, Rothwell U.D. 3, Bradford C.B. 2), Lancashire 14 (Manchester C.B. 6, Preston C.B. 2), London 10 (Bethnal Green 2, Stepney 2), and Devonshire 6 (Plymouth C.B. 6).

The largest centres of dysentery were Yorkshire West Riding 84 (Leeds C.B. 26, Barnsley C.B. 16), Lancashire 65 (Liverpool C.B. 16, Kirkby U.D. 13), London 64 (Islington 12, Deptford 10), and Warwickshire 34 (Coventry C.B. 20, Birmingham C.B. 12).

Fewer in Mental Hospitals

The number of patients in mental hospitals in England and Wales again fell in 1957, according to the Annual Report to the Board of Control (H.M.S.O., 9d.). There were 2,518 fewer than twelve months before, and at 146,962 the total was the lowest since 1949. But the rate of admission continues to increase. Last year admissions numbered 88,943 (45% readmissions), compared with 83,994 in 1956 and 55,856 in 1950. While voluntary admissions increased, admissions under certificate were fewer. In 1956, 78% of the admissions to designated mental hospitals were voluntary and 20% were under certificate. During 1957, voluntary admissions increased to 83%, and certified cases fell to 16%. Of the 82,778 patients discharged, 19,643 were listed as recovered, 54,054 were relieved, and 8,822 showed no improvement.

The number of student nurses in mental hospitals (excluding mental deficiency hospitals) continued to increase during the year, but a serious shortage of nursing staff remained. Whole-time staff numbered 20,903 and part-time staff 7,176 at the end of September, 1957, as compared with 20,358 and 6,937 a year earlier.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **September 20** (No. 38) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	2	0	2	0	3	3	0	5	0	
Dysentery	410	63	169	12		174	22	100	6	4
Encephalitis, acute	5	0		0		1	0		0	
Enteric fever:										
Typhoid	6	3	1	1	1	6	0	1	0	0
Paratyphoid	5	3	1(B)	1	3(B)	19	0	0	0	
Food-poisoning	369	41	21	1		240	18	10	0	
Infective enteritis or diarrhoea under 2 years				14	44				10	31
Measles*	1,470	100	26	8	37	1,044	28	15	25	18
Meningococcal infection	9	2	8	0		30	2	6	1	
Ophthalmia neonatorum	17	3	2	0		26	0	3	0	
Pneumonia†	175	11	90	0	1	702	15	266	3	
Poliomyelitis, acute:										
Paralytic	48	2	17	1	10	113	7	7	6	
Non-paralytic	31	1				85	4			
Puerperal fever.§	226	40	12	1		248	41	5	1	
Scarlet fever	434	24	61	26	17	321	28	60	28	18
Tuberculosis:										
Respiratory	458	44	62	17		522	47	83	11	
Non-respiratory	62	6	14	4		54	4	10	5	
Whooping-cough	718	36	69	47	10	724	46	45	2	5

DEATHS	1958 Eng. & Wales	1958 Lond.	1958 Scot.	1958 N. Ire.	1958 Eire	1957 Eng. & Wales	1957 Lond.	1957 Scot.	1957 N. Ire.	1957 Eire
Diphtheria	0	0	0	0	1	No comparable figures available.	0	0	0	0
Dysentery	0	0		0			0		0	0
Encephalitis, acute		0			0		0			
Enteric fever	0	0	0	0			0	0	0	0
Infective enteritis or diarrhoea under 2 years	6	1	0	0	0		0	0	0	0
Influenza	3	0	0	0	0		2	5	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		1	0				0	1		
Pneumonia	304	19	4	7	9		21	19	13	2
Poliomyelitis, acute	1	0	1	0	0		2		0	0
Scarlet fever		0	0	0	0		1	0	0	0
Tuberculosis:										
Respiratory	46	3	4	1	2		6	3	1	4
Non-respiratory		1	1	0	0		0	1	0	1
Whooping-cough	2	0	0	1	0		0	0	0	0
Deaths 0–1 year	288	33	21	3	9		24	25	7	13
Deaths (excluding stillbirths)	7,889	621	443	89	130		683	579	104	126
LIVE BIRTHS	13,725	1178	969	204	353		1201	896	224	369
STILLBIRTHS	331	33	18				15	19		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

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(*Medical Times* 1958, **1**, 74)

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Antacids. *The Practitioner*, January 1957, **178**: 43

Antacids in Peptic Ulcer. *The Practitioner*, January 1956, **176**: 103

Recent Advances in the Ulcerative Diseases of the Gastrointestinal Tract. *Amer. J. Gastro.*, December 1956, **26**: 665

Ambulatory Continuous Drip Method in the Treatment of Peptic Ulcer. *Amer. J. Dig. Dis.*, March 1955, **22**: 67-71

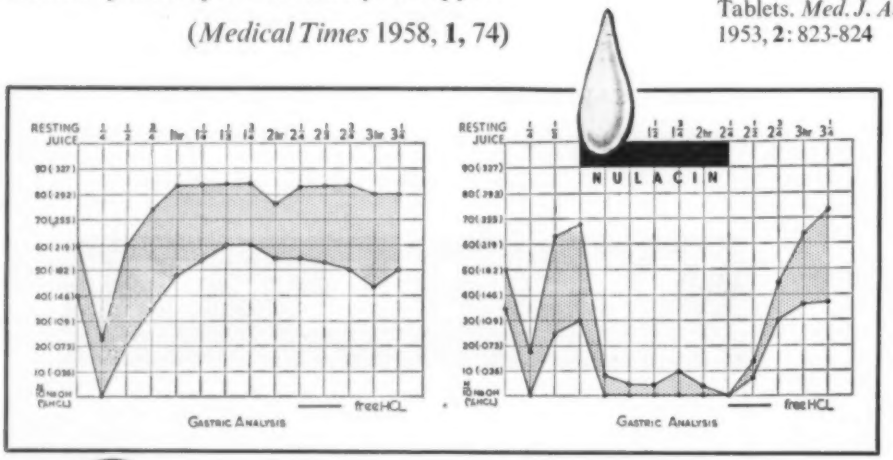
Management of Peptic Ulceration in General Practice. *Med. World*, December 1954, **81**: 591-601

Clinical Investigation into the Action of Antacids. *The Practitioner*, July 1954, **173**: 46

Further Studies on the Reduction of Gastric Acidity. *Brit. Med. J.*, 23rd January 1954, **1**: 183-184

Control of Gastric Acidity by a New Way of Antacid Administration. *J. Lab. & Clin. Med.*, 1953, **42**: 955

The Effect on Gastric Acidity of "Nulacin" Tablets. *Med. J. Aust.*, 28th November 1953, **2**: 823-824



Nulacin tablets have no B.P. equivalent and have been classified in categories 3 & 4 by the Joint Committee on Prescribing.

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Medical News

Insurance for Private G.P. Treatment.—The Fellowship for Freedom in Medicine has persuaded the British United Provident Association to launch an insurance scheme to help cover the cost of private treatment by general practitioners. Details of the scheme, which will come into operation on January 1, are due to be announced next month. While there already exist several excellent schemes for providing cover against the costs of treatment in a hospital or nursing-home and of specialist advice and investigation—such as those of B.U.P.A. itself, the London Association for Hospital Services (Hospital Service Plan), and the Western Provident Association—this is the first insurance scheme to offer cover in Britain against the cost of private treatment by a general practitioner. The new cover will be an option restricted to those already insured under B.U.P.A.'s standard scheme (for private beds, specialist fees, etc.), whereby for an additional rate a subscriber may obtain cover for himself and his dependants for attendance by a private general practitioner and for minor operations; as yet, the cost of drugs is not able to be included. The basic annual rates for a single subscriber (with additional rates for dependants) are on two scales: Scale A is £2 10s., allowing a payment of 12s. 6d. towards the G.P.'s fee; Scale B £4 15s., allowing a payment of 20s. Further information may be obtained from the B.U.P.A. offices at Provident House, 24–27, Essex Street, London, W.C.2, early in November. In the Channel Islands the Western Provident Association has a special scheme which includes insurance cover for private practitioners' fees, and it appears that this company is now thinking of following B.U.P.A.'s lead and offering a scheme applicable to Britain.

Restrictive Practices.—On October 6, at its first hearing, the Restrictive Practices Court began the examination of an agreement between all members of the Chemists' Federation. The main restriction before the Court was one whose principal purpose, according to the Federation, is to restrict the sale to the public of proprietary medicines to retail chemists and pharmacists. This, the Federation submitted, is not contrary to the public interest. The hearing arose from a reference by the registrar of restrictive trading agreements, under section 20 of the Restrictive Trade Practices Act, 1956 (*The Times*, October 7).

Middlesex Hospital.—Details of the new Middlesex Hospital Medical School were given by the dean, Professor B. W. Windeyer, at the school's annual dinner at the Savoy Hotel on October 3. He announced that the school council had decided to name the residential college after Lord Astor and to call the large lecture theatre the Edward Lewis theatre. The latter is included in the first phase, now under construction. The dean said it would accommodate 180 and would be available for undergraduate meetings; it would have a fully equipped stage. The second-phase building was planned to give maximum flexibility for changes that might be necessary in the light of changing demands of teaching and research. It would complete the premedical and preclinical departments, and would also provide an improvement in school amenities and accommodation for the student health service. The third stage would be the residential college for 150 students.

King's College Hospital.—The annual dinner of past and present students of King's College Hospital was held at the Savoy Hotel on October 4. Dr. Sydney Thomson presided over a large gathering. Dr. K. E. D. Dauncey proposed the toast of the Medical School and paid a tribute to the work of the dean, Dr. V. F. Hall, who gave a good report on the school. Sir Cecil Wakeley proposed the toast of the chairman and Dr. Thomson replied. On October 1 new medical and surgical units were inaugurated at the school. Dr. Clifford Hoyle has been appointed part-time director of the medical unit, and Mr. Harold Edwards part-time director of the surgical unit.

Accidents to B.M.A. Members.—Details of the special accident insurance scheme available to B.M.A. members are given at p. 11 of the advertisements. The scheme was first announced at this year's Representative Meeting, and was welcomed in this *Journal* as "a new and most valuable practical benefit of membership of the B.M.A." (*Journal*, July 19, p. 150).

Symposium on Response to Injury.—Immediately following the Fourth International Congress of Biochemistry (*Journal*, September 20, p. 738), an international symposium on the biochemical response to injury was held under Dr. D. P. Cuthbertson's chairmanship at Semmering, in Austria, from September 7 to 12. It was attended by 24 research workers from nine countries, and the proceedings are to be published by Blackwell Scientific Publications Ltd. The symposium was organized by the Council for International Organizations of Medical Sciences with assistance from the Wellcome Trust and the International Union of Biochemistry.

New Medical Films.—Films recently released by pharmaceutical houses include "Simplified Urine Analysis," sponsored by Messrs. Ames Company (London) and introduced at its first showing on October 2 at the Royal Society of Medicine by Sir Cecil Wakeley; "Management of Twins in Pregnancy and Labour" and "Routine Use of Ergometrine in the Third Stage of Labour," produced by the Wellcome Foundation's film unit and introduced at their first showing on October 8 by Professor W. C. W. Nixon; and "Prostatectomy under 'Fluothane,'" released by Imperial Chemical Industries Ltd. All these films are 16 mm. with colour and sound. Further details may be obtained from the sponsoring firms.

General Nursing Council.—Among those appointed by the Minister of Health to the General Nursing Council for England and Wales for the next five years are the following: Mr. P. H. Constable, secretary and house governor, St. George's Hospital, London; Dr. Alexander Walk, physician superintendent, Cane Hill Hospital, Coulsdon; Dr. John Douglas, M.O.H. of Bradford; and Mr. Basil Hume, formerly senior surgeon, St. Bartholomew's Hospital, London.

International Scientific Unions.—The Royal Society's delegation to the eighth general assembly of the International Council of Scientific Unions in Washington, October 2–6, was led by Sir Rudolph Peters and included Professor A. V. Hill. The council is concerned with plans for the International Geophysical Year, future Antarctic research, and space research.

Polar Medal.—Colonel R. A. Smart, R.A.M.C., leader and medical officer of the Royal Society Antarctic Expedition for the International Geophysical Year, has been awarded a polar medal.

COMING EVENTS

Nurses and Midwives Conference.—Annual conference and the London Nursing Exhibition, October 13–17 at the Seymour Hall, London.

Annual Service for Doctors, Nurses, and Allied Professions.—Sunday, October 19, at 3 p.m. at Trinity Presbyterian Church, Unthank Road, Norwich. The preacher will be the Lord Bishop of Norwich.

Leeds University, Faculty of Medicine.—The Bishop of Bradford will give the inaugural lecture at 3 p.m. on October 20. His subject will be "The Wholeness of Man."

Abortion Law Reform Association.—Public meeting, 7.15 p.m. on October 22 at Caxton Hall, Westminster, on "Our New Bill." Details from the secretary, 18, Wyatt Park Road, London, S.W.2.

27th General Hospital.—Annual reunion dinner at the Eccleston Hotel, London, S.W.1, October 25, at 7.15 p.m. Tickets (25s. inclusive) may be obtained from Mr. G. Pudney, 161, Silverleigh Road, Thornton Heath, Surrey.

Recent Advances in Cancer.—Week-end symposium for junior consultants, S.H.M.O.s, and senior registrars, October 25 and 26 at the Royal Marsden Hospital. Further details from the department of clinical studies, Royal Marsden Hospital, Fulham Road, London, S.W.3.

Faculty of Radiologists.—Provincial meeting in Sheffield on October 25. Details from Captain T. W. BARNARD, "Broom Cross," Tree Root Walk, Sheffield, 10.

Thomas Vicary Lecture.—Sir JOHN MCNEE will lecture on October 30 at 5 p.m. at the Royal College of Surgeons of England on "Barber-Surgeons in Great Britain and Ireland."

Association of Anaesthetists of Great Britain and Ireland.—Annual meeting, October 30 to November 1 in Southport. Further details from the honorary secretary, 47, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, October 13

BRISTOL YOUNG DOCTORS GROUP.—At Board Room, Bristol Royal Infirmary, 8 p.m., discussion: G.P. Trainee Scheme.

EDINBURGH UNIVERSITY.—At Anatomy Lecture Theatre, University New Buildings, 5 p.m., Inaugural Lecture by Professor W. L. M. Perry: Pharmacology and the Practice of Medicine.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 4.30 p.m., guest lecture by Professor Chassar Moir: Some Thoughts on the Technique of Caesarean Section.

LONDON UNIVERSITY.—At Physiology Lecture Theatre, St. Bartholomew's Hospital Medical College, 5.30 p.m., special university lecture in physiology by Professor W. F. Hamilton, Ph.D. (Georgia): Measurements of the Cardiac Output.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. F. B. Cockett: Post-thrombotic Syndrome of the Leg; 6.30 p.m., Mr. Clive Butler: Carcinoma of the Colon.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—5 p.m., Bengué Memorial Award Lecture by Dr. B. G. B. Lucas: Artificial Aids in the Control of the Circulation (illustrated).

Tuesday, October 14

HEATHERWOOD ORTHOPAEDIC HOSPITAL.—8.30 p.m., Professor G. Perkins: Radiodiagnosis of Bone Diseases.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. R. H. Meara: Sweat Production and Anomalies.

●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—(1) At Hammersmith Hospital, 2 p.m., guest lecture by Colonel P. H. Addison: Legal Hazards in Obstetrics and Gynaecology. (2) At Hammersmith Hospital, 3 p.m., guest lecture by Professor C. V. Harrison: Obstetric Anuria.

LONDON UNIVERSITY.—At Physiology Lecture Theatre, St. Bartholomew's Hospital Medical College, 5.30 p.m., special university lecture in physiology by Professor W. F. Hamilton, Ph.D. (Georgia): Regulation of the Cardiac Output.

MANCHESTER MEDICAL SOCIETY.—(1) At Large Anatomy Theatre, Medical School, Manchester University, 4 for 4.30 p.m., University Lecture on the History of Medicine by Professor W. I. C. Morris: John and William Hunter, and their Polemics. (2) SECTION OF SURGERY.—At Staff House, Manchester University, 7.45 for 8 p.m., Presidential Address by Mr. H. T. Cox: Dumping Syndrome.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. H. C. Edwards: Disorders of the Jejuno-ileum; 6.30 p.m., Mr. W. P. Cleland: Surgical Treatment of Acquired Valvular Disease of the Heart.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Professor Gordon Lennox: Modern Treatment of Heart Disease in Pregnancy.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Dr. T. Rowland Hill: neurological demonstration.

Wednesday, October 15

BRITISH ASSOCIATION OF SPORT AND MEDICINE.—At Charing Cross Hospital Medical School, 5.30 p.m., Mr. Frank Law and Mr. M. J. Roper-Hall: Vision in Sport.

COLLEGE OF GENERAL PRACTITIONERS: NORTHERN HOME COUNTIES FACULTY.—At Lecture Theatre, St. Bartholomew's Hospital Medical College, 9 p.m., second annual Pfizer Lecture by Dr. E. F. Scowen: Some Difficulties in Prescribing.

EUGENICS SOCIETY.—At Royal Society, Burlington House, W., 5.30 p.m., Dr. Christopher Tietze: Human Fertility—Statistical Considerations.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. H. Haber: Histology of Normal Skin.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. A. B. Paterson: Development and Detection of Tuberculin Sensitivity.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. A. H. Harkness: Non-gonococcal Urethritis.

LIVERPOOL UNIVERSITY: FACULTY OF MEDICINE.—At Large Lecture Theatre, New Medical School, Ashton Street, 5.15 p.m., Professor I. F. S. Mackay (Jamaica): Measurement of Arterial and Venous Valvular Incompetence.

LONDON UNIVERSITY.—At Physiology Lecture Theatre, St. Bartholomew's Hospital Medical College, 5.30 p.m., special university lecture in physiology by Professor W. F. Hamilton, Ph.D. (Georgia): Experimental Congestive Failure of the Circulation.

MANCHESTER MEDICAL SOCIETY.—At New Union Buildings, Oxford Road, 8.15 to 11 p.m., reception for Fellows and friends.

●MIDLAND MEDICAL SOCIETY.—At Birmingham Medical Institute, 7 for 7.30 p.m., annual dinner. 8.45 p.m., Address by Dr. T. F. Fox (Editor, the *Lancet*): Rewards and Fairies.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., guest lecture by Dr. D. J. Bell: Carbohydrate Metabolism.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Mr. C. P. Wilson: Diverticula of the Pharynx.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. Sol M. Cohen: Place of Sympathectomy Procedures; 6.30 p.m., Mr. John Charnley: Fractures of the Femur.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine, 8.45 p.m., Professor C. G. Rob: Arterial Reconstruction and its Effect on General Medicine.

Thursday, October 16

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At Beveridge Hall, Senate House, 5.30 p.m., Sir Edward Salisbury, F.R.S.: Influence of Botany on Health and Disease.

HONYMAN GILLESPIE LECTURES.—At Anatomy Theatre, University New Buildings, Teviot Place, Edinburgh, 5 p.m., Dr. D. V. Hubble: Auto-immunizing Thyroiditis.

HYPNOTHERAPY GROUP.—At Royal Society of Medicine, 8 p.m., Dr. Lindesay Neustatter: Homosexuality.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8 p.m., Dr. Jean Mackintosh: Future of Medical Women in the Public Health Service.

NORTH-WESTERN THORACIC SOCIETY.—At Clinical Science Buildings, Manchester, 5 p.m., Presidential Address by Dr. Robert Coope: Sundry and Manifold Changes.

ROYAL ANTHROPOLOGICAL INSTITUTE, 21, Bedford Square, London, W.C., 5.30 p.m., Dr. H. Lehmann: Abnormal Haemoglobins.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. H. R. I. Wolfe: Testicular Tumours; 6.30 p.m., Mr. Ashton Miller: Diverticula of the Bladder.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., 1st Manson Oration by Sir Philip Manson-Bahr: The March of Tropical Medicine During the Last Fifty Years.

Friday, October 17

BRITISH INSTITUTE OF RADIOLOGY.—Radiobiology Meeting, 2 to 4 p.m., papers by Dr. J. R. Munson, Miss T. Alper, Dr. N. E. Gillies, Dr. S. R. Pelc, and Dr. W. B. Looney (U.S.A.). 4.15 to 5.30 p.m., papers by Dame Janet Vaughan and Dr. Maureen Owen and Mr. D. M. Taylor.

EDINBURGH UNIVERSITY.—At Anatomy Lecture Theatre, University New Buildings, 5 p.m., Inaugural Lecture by Professor J. I. P. James: Evolution of Orthopaedic Surgery.

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. B. Mitchell-Heggs: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. E. H. Hudson: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners by Mr. N. Asherson: Deafness

KENT AND CANTERBURY HOSPITAL.—8 p.m., clinical meeting.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.45 p.m., Mr. S. G. Browne (Congo Belge): Sunshine and Shadow in the African Equatorial Forest.

MANCHESTER MEDICAL SOCIETY: SECTION OF ANAESTHETICS.—At Clinical Sciences Building, York Place, 4.30 for 5 p.m., joint meeting with North of England Society of Obstetricians and Gynaecologists. Dr. A. Mackenzie, Dr. E. G. Rees Jones, Dr. H. E. Pooler, Dr. Trevor Johnson, Mr. O. Vaughan Jones, and Professor T. N. A. Jeffcoate: Anaesthesia in Obstetrics.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—10 a.m., guest lecture by Professor G. Hadfield: Hormonal Control of Normal Mammogenesis.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5.15 p.m., Mr. G. C. Knight: Cervical Disk Lesions; 6.30 p.m., Mr. Ralph Shackman: Non-tuberculous Urinary Infections.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., joint meeting with Medico-Chirurgical Society of Edinburgh, discussion: Relative Importance of the Scientific and the Clinical in Medical Training. Openers, Professor M. Woodruff, Mr. Robert Maller, and Dr. J. D. S. Cameron.

Saturday, October 18

BIOCHEMICAL SOCIETY.—At Chemistry Lecture Theatre, Royal College of Science, 2 p.m., 376th meeting.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Preston Hall Chest Hospital, Maidstone, 10.30 for 11 a.m., Mr. R. H. F. Brain: Oesophageal Disease and the Lung; Dr. G. R. W. N. Luntz: Diabetes and Tuberculosis; Dr. E. R. Jones and Dr. A. Golebiowski: Demonstration of Pulmonary Function Tests; 2.30 p.m., annual general meeting.

Sunday, October 19

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—10.15 a.m., to 12.30 p.m., seminar. Mr. A. Radcliffe: Common E.N.T. Conditions.

MANCHESTER UNIVERSITY: FACULTY OF MEDICINE AND NORTH-WEST ENGLAND FACULTY, COLLEGE OF GENERAL PRACTITIONERS.—At Theatre 1, Clinical Sciences Building, York Place, 11 a.m., demonstration by Dr. J. F. Wilkinson: Blood Disorders.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Emson.—On September 7, 1958, at the University Hospital, Saskatoon, Canada, to Mary (formerly Lewis) and Dr. Harry E. Emson, a daughter—Susan.

DEATHS

Howlett.—On September 16, 1958, at his home, Wimbledon, London, S.W., Michael Joseph Howlett, M.B., B.Ch.

Jones.—On September 19, 1958, the result of a road accident, Pauline Miriam Jones, M.B., B.Chir., of 16, Elmsleigh Road, Weston-super-Mare, Somerset.

Keeling.—On September 20, 1958, at 12, Clevedon Road, Tilehurst, Reading, Berks, George Sydney Keeling, M.D., formerly of Attleborough, Norfolk, aged 85.

Otway.—On September 19, 1958, at Londonderry, Alexander Loftus Otway, M.B., B.Ch., D.P.H., Lieutenant-Colonel, R.A.M.C. (retired).

Rae.—On September 17, 1958, at Fownhope, Bromsgrove, Worcs, Arthur Joseph Rae, M.R.C.S., L.R.C.P., aged 79.

Richard.—On September 15, 1958, in London, Kurt Simon Richard, M.R.C.S., L.R.C.P., of Welwyn Garden City, Herts.

Timms.—On September 15, 1958, at the Royal East Sussex Hospital, Hastings, Charles Gordon Timms, O.B.E., *M.C.*, L.R.C.P.&S.Ed., L.R.F.P.S.

Trubshaw.—On September 15, 1958, at Curfew, Llanelltyd, Dolgelley, Merioneth, Kenneth Vincent Trubshaw, M.B., F.R.C.S.Ed., aged 81.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Maternal Virus Infections and Congenital Heart Disease

Q.—*What is the present view on the relationship between the incidence of congenital heart disease and maternal virus infections during pregnancy ?*

A.—It is generally accepted that there is a direct association between rubella and congenital cardiac malformations. In two British series[1,2] the number of children with congenital heart disease was 3 in 11 when the mother contracted rubella in the first month of pregnancy, and 1 in 18 for the next two months of pregnancy. The cardiac malformations that occur particularly are patent ductus arteriosus (often with pulmonary stenosis) and ventricular septal defect. Rubella, however, probably accounts for only about 2% of all cases of congenital heart disease. No other maternal virus diseases have been definitely shown to be responsible for congenital cardiac malformations.

References

1 Hill, A. B., Doll, R., Galloway, T. McL., and Hughes, J. P. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 1.
2 Brown, C. M., and Nathan, B. J., *Lancet*, 1954, **1**, 975.

"Nivembin" for Amoebiasis

Q.—*What is the value of nivembin (chloroquine sulphate and di-iodohydroxyquinoline) in the treatment of amoebiasis ?*

A.—Chloroquine is a good drug for the treatment of hepatic amoebiasis, a condition which occurs in acute form in association with amoebic dysentery and, in more chronic form, associated with abscess formation after an interval, which may be prolonged, following an alimentary amoebic infection. In the latter case, however, an intensive course of chloroquine or emetine would be required, probably together with aspiration of pus from the liver. Nivembin would not be a satisfactory drug for the treatment of such cases.

Di-iodohydroxyquinoline is of moderate usefulness in the treatment of patients passing cysts as the result of a subacute or chronic infection with *Entamoeba histolytica*. The relapse rate following such treatment is higher than that which follows the use of some other amoebicides. It therefore follows that nivembin has but limited application, for its di-iodohydroxyquinoline fraction is of very little value in acute amoebic dysentery in which the liver may be acutely infected and therefore apt to be benefited by the chloroquine constituent of the compound. On the other hand, in patients suffering primarily from amoebic abscess of the liver more chloroquine is required than can properly be given in the form of nivembin. The compound is another example of a blunderbuss remedy which aims to do two things, neither of which it does adequately.

Treatment of Chronic Prostatitis

Q.—*What is the treatment for chronic prostatitis when no organisms have been isolated and the patient has had no chemotherapy ?*

A.—Treatment depends largely on the type of chronic prostatitis which is present. If it is a catarrhal chronic prostatitis, with a diffusely enlarged and uniformly boggy gland in which the prostatic secretion contains only a moderate number of pus cells, it is essential to prevent pelvic congestion and overaction of the prostate gland. Prostatic massage at fortnightly intervals combined with one of the long-acting sulphonamide drugs should clear up the chronic catarrh. Should massage be unsuccessful short-wave diathermy or rectal diathermy may succeed. If the purulent type of prostatitis is present, in which the gland is irregular with alternating areas of induration and bogginess, there will be numerous pus cells in the prostatic secretion. Prostatic massage at weekly intervals will drain the acini of pus, and the number of pus cells in the secretion will indicate the efficacy of the treatment. The seminal vesicles must be included in the massage, as they are invariably involved in the infection. Any organisms which may be cultured from the secretion must be typed for sensitivity and the appropriate antibiotics prescribed. If this type remains resistant to massage, diathermy may be tried, failing which a minimal perurethral resection to open up occluded prostatic ducts has proved successful in very resistant cases. It would be advisable to make sure that prostatic calculi are not maintaining infection. A radiograph of the pelvis would exclude calculi, while a urethral stricture, which may also initiate and maintain prostatic infection, should be excluded by urethrogram. If the infection has been present for some time and has become "burnt out," scar tissue replacing the inflammatory process, the sclerotic type of chronic prostatitis results. The gland is small and hard, the prostatic urethra is narrowed, and the bladder neck obstructed. In these cases a perurethral resection is indicated.

Life of the Tapeworm

Q.—*What is the duration of life of a tapeworm if no treatment is given or if successive treatments fail ?*

A.—Tapeworms in general have long lives, and instances have been known in which untreated worms have lived for 15 to 16 years. No evidence is available on whether a worm's life is shortened by repeated treatment which fails to expel it from its host, but there is no reason to suppose that it is.

Fantus Test

Q.—*What is the Fantus test for estimating urinary chloride excretion ?*

A.—Fantus's test is performed as follows. Using a dropping pipette, place 10 drops of approximately neutral urine and 1 drop of 20% potassium chromate in a test-tube. Wash the pipette out thoroughly with distilled water. Take into the pipette 2.9% silver nitrate and add dropwise to the urine while shaking. Count the number of drops needed to change the colour to brick red. This number expresses in grammes the content of sodium chloride per litre of urine.

Physiological variations in urinary *p*H are not important, but strongly alkaline urine due to, e.g., cystitis should be approximately neutralized with acetic acid before use.

References

1 Fantus, B., *J. Amer. med. Ass.*, 1936, **107**, 14.
2 Harrison, G., *Chemical Methods in Clinical Medicine*, 1957, 4th ed., chap. 15, p. 310. Churchill, London.

Undulant Fever

Q.—*What is the treatment for undulant fever ?*

A.—Brucellosis or undulant fever has been successfully treated by sulphonamides, streptomycin, the tetracyclines, chloramphenicol, erythromycin, and novobiocin, but relapses are apt to follow treatment. Whereas extracellular brucella organisms are readily destroyed by antibiotics, intracellular organisms develop a satisfactory *modus vivendi*, finding a suitable medium for multiplication and protection against lethal phagocytosis and against antibiotics. This successful intracellular parasitism accounts for persistence and relapses of the infection despite treatment. Increased therapeutic success depends upon the future development of chemotherapeutic agents which penetrate the host cell easily and without injury or by some method of dislodging organisms from their intracellular position.

Initially, tetracycline should be given in doses of 2 g. daily for two weeks. Relapses, as they occur, may be controlled by further courses or by giving streptomycin in daily intramuscular doses of 2 g. together with tetracycline.

Alternatively, novobiocin may be used in daily oral doses of 2 g. for two weeks. In view of the numerous antibiotics now available for ringing the changes, it is often overlooked that brucellosis is a self-limiting disease and that most patients are free from the infection within a few months. Some continue to have symptoms during convalescence and need firm reassurance rather than further chemotherapy, unless a recurrence of fever heralds a relapse. This should be treated along the lines outlined above.

Occult Blood in Urine

Q.—*What are the relative merits of a chemical test for the presence of occult blood in the urine, such as the "occultest" tablets made by Ames and Co., and routine microscopic examination of deposit as a screening check on each urine specimen?*

A.—The tests for blood in urine were compared by Caplan and Discombe.[1] They record that the *o*-tolidine test, such as used in occultest tablets, will detect 5×10^4 cells per ml., equivalent to 0.15 mg. haemoglobin per 100 ml. urine: this figure has been confirmed by other workers. Routine microscopic examination of a centrifuged deposit will detect between 10^5 and 10^6 cells per ml. according to the details of the technique: if 12.5 ml. urine is centrifuged, 12 ml. removed, the cells resuspended in the residual 0.5 ml. and examined in a Fuchs–Rosenthal chamber, red blood cells will be detected when not more than 1,000 per ml. are present. If a drop of the deposit is placed between ordinary slide and coverglass the limiting frequency will be ten times greater—i.e., about 10,000 per ml.

References

1 Caplan, H., and Discombe, G., *Brit. med. J.*, 1951, **2**, 774.

NOTES AND COMMENTS

Treatment for Roundworms.—Dr. L. G. Goodwin (Wellcome Laboratories of Tropical Medicine, London, N.W.1) writes: I raised the point on toxaemia and fluid balance ("Notes and Comments," August 16, p. 462) because too little attention has been given to this aspect of treatment. In territories such as the west coast of Ceylon, where roundworm infection is heavy, it is not at all uncommon for children to be admitted to hospital with "toxaemia" and convulsions caused by *Ascaris* without the classical signs of intestinal obstruction. Attention to fluid balance and a dose of piperazine (which narcotizes the worms and does not stimulate them) is often sufficient to bring about recovery. I recently saw two cases treated in this way by Dr. Stanley de Silva at the Lady Ridgeway Hospital in Colombo. The patients are usually pitiable, ill-nourished children who are very poor surgical risks. Sappenfield, Swartzwelder, and Miller[1] reported the successful use of piperazine given by intestinal tube in cases of partial intestinal obstruction caused by roundworms. Roundworms produce an evil-smelling secretion which can be smelt in the breath of heavily infected persons. Rashes and other sensitization phenomena are not uncommon in infected people in the tropics; many laboratory workers who handle the worms for any length of time become allergic to constituents of *Ascaris*. It is likely that some (though not all) cases of tropical eosinophilia are associated with *Ascaris* infection. It seems to me that *Ascaris* toxaemia requires more study, and it would be of value to have the views of physicians working in areas of heavy roundworm endemicity.

Reference

1 Sappenfield, R. W., Swartzwelder, C., and Miller, J. H., *Amer. J. trop. Med. Hyg.*, 1957, **6**, 383.

Our Expert replies: Dr. Goodwin is shifting his ground and raising issues which bear little relation to the original question ("Any Questions?" July 26, p. 260) or to his first comments on the answer given to that question. He then stated: "Small children are sometimes admitted to hospitals in the tropics with toxaemia, vomiting, and convulsions caused by massive *Ascaris* infections. These patients are often severely dehydrated. . . ." He now implies that attention to fluid balance is not uncommonly necessary even in the absence of vomiting or massive infections. Unless some degree of intestinal obstruction is present, however, it is very rare for children suffering only from ascariasis to be dehydrated. At all large hospitals in areas in which the infection is endemic many thousands of children will be encountered in whom a heavy *Ascaris* infection is present yet in whom no dehydration or manifest signs of toxaemia are found, and the vast majority can be treated without more attention to fluid balance than is given to patients in general. Indeed, Dr. Goodwin indicates that factors other than ascariasis are probably playing some part in the production of the children's condition, for he mentions their pitiable, ill-nourished state. He also states that they constitute poor surgical risks. This implies that surgery has to be considered in such cases, and this implication accords ill with the contention that dehydration is the result of a non-massive infection in the absence of some degree of intestinal obstruction. The causal relationship between convulsions and toxaemia resulting from ascariasis which Dr. Goodwin assumes is doubted by very many workers in this field. Larval forms of the worm may occasionally reach the brain during their migratory phase, and consequently give rise to an epileptiform attack, but toxaemia produced by worms resident in the intestine cannot be accepted as a proved cause of convulsions. The cause of a convulsion may require detailed elucidation, and it is quite unjustifiable to implicate an *Ascaris* infection merely because such an infection happens to be present.

Brucella Abortus in Milk.—Dr. H. R. E. Wallis (Bath) writes: Dr. J. M. Ross ("Notes and Comments," September 20, p. 754) clarifies the position from the point of view of the medical officer of health, but I should like to contest his statement that "the evidence suggests that most current cases of undulant fever are not due to ingestion of infected milk but to contact with infected material from occupational or other circumstances." This may be true in America, where many cases occur in people who handle meat, where better care is taken of milk than in this country, and where most of the published work appears. Reports in this country are few and far between, but during the past 20 years two milk-borne epidemics have been reported.[1,2] Barrett and Rickards[3] recorded 25 cases, of which 11 had no direct contact with infection, and in the other 14 milk may have been responsible. Davies[4] reported 11 cases, of which seven were considered to be due to drinking raw milk, and in my own series[5] of 10 cases in children there was only one who might have derived his infection from direct contact. Lastly, Dalrymple-Champneys,[6] in his masterly review, considered 907 patients and found that only 123 had been specially exposed to direct contact with infected material, and in only 34 of these did he consider that was the probable mode of infection. This may seem an unimportant point, but it does serve to emphasize that raw milk is not safe even if it has a nice label saying "Tuberculin-tested" and a gold top to the bottle.

References

1 Elkington, G. W., Wilson, G. S., Taylor, J., and Fulton, F., *Brit. med. J.*, 1940, **1**, 477.
2 Cruickshank, J. C., and Stevenson, G. A., ibid., 1942, **1**, 522.
3 Barrett, G. M., and Rickards, A. G., *Quart. J. Med.*, 1953, **22**, 23.
4 Davies, J. E., *Brit. med. J.*, 1957, **2**, 1082.
5 Wallis, H. R. E., ibid., 1957, **1**, 617.
6 Dalrymple-Champneys, W., *Lancet*, 1950, **1**, 429, 477.

Correction.—Professor L. F. Larionov (Institute of Experimental Pathology and Therapy of Cancer, Moscow) writes to say that the four patients he described as being active and well after 9–10 years of maintenance chemotherapy (*Journal*, July 19, p. 160) were suffering from Hodgkin's disease, *not* leukaemia as stated in our report.

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